Antimicrobial Therapy in Medical Practice

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AFFECTIONATELY DEDICATED

to my friend and colleague

GEORGE MORRIS PIERSOL, M D

Foreword

Of Making Many Books

Or rather for the moment, about the making of this one I am pleased to be allowed to air some views in writing this prologue It is a valuable timely and much needed book, that offers to all physicians within its convenient scope a wealth of practical material, the critical evaluation of that material by expert authors and their sage advice on its long range use

One cannot overestimate the importance to Man of the victories gained by our new weapons over many diseases of microbial origin even though it is yet too soon to foresee or assess the full impact of those victories on all aspects of human affairs But, to make the most effective use of those weapons, we must know the indications for and the manner of their use as well as the principles that underlie their action. The first emphasis therefore lies on making a diagnosis in sufficient detail to permit the selection of the proper therapeutic agent and then on the effective use of that agent. Between the covers of this book the practitioner will find the nuggets of information that have been culled for him from a vast literature (which he could never hope to scan) and that have been tried and assayed for him in the rich experience of the authors

Potent weapons improperly used, can do serious damage in unskilled hands The physician must never lose sight of the basic principle that his treatment should not do the patient an avoidable harm The authors have kept this concept ever in mind and have stressed the possible dangers and pitfalls with clarity and commendable zeal. Let me

record my concern over the commonest iatric sin against the individual patient The use of these powerful weapons in treating minor ailments This robs him of his ability to stand on his own immunologic legs as a result of repeated lesser encounters with microbial agents What is worse, it may in duce a serious sensitivity to a therapeutic agent that would preclude its use in a later major illness in which that agent might have been life-saving. One should not shoot sparrows with rockets carrying atomic war heads.

There is a yet more serious aspect to the injudicious and excessive use of these agents that applies to Man in gen eral The production of drug resistant strains Within a few years the staphylococci met in hospitals have shown a shift from twenty per cent so resistant to seventy-five per cent. The tubercle bacillus has shown amazing aptitude in this direction. Just because we have not yet witnessed any sig nificant trend toward the development of organisms resistant to penicillin does not preclude that possibility Indeed, quite the reverse is to be expected, in the light of what is known of the mechanism of action of all such agents. To be an effective antimicrobial agent, a drug must be able to *interfere with some part of a function that is vital* to the organism, yet sufficiently remote from the most fundamental life processes to imply the possibility that the function can be by-passed. As Fleming pointed out, 'Because some of the bacteria have the power of making themselves resistant to all antibiotics it is essential that these drugs shall not be abused.

It is, *therefore to be deplored* that mass administration of drugs to well persons is gaining favor in some quarters in attempts to prevent certain infections in controlled populations Over a decade ago such a use of sulfonamides resulted in drug resistant strains of streptococci in a place

where they wreaked havoc a few months later Today peni cillin is being given parenterally in a similar group to pre vent rheumatic fever There is already being harvested a crop of unjustified penicillin sensitivities and who knows what else may be in the making We physicians of today carry the responsibility that in the year 2055 when some future authors write a book on *Antimicrobic Therapy* the Foreword shall not refer to the curious fact that about a century ago Man thought he had conquered microbes with substances called antibiotics but by their unwise over use had raised up new and resistant strains, whose study was now the major weariness of his flesh. But, those who prefer to ignore history must be prepared to repeat it, as the phi losopher Santayana pointed out.

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Preface

THE practice of medicine offers no greater satisfaction than the successful treatment of a patient with a severe infection which prior to modern antimicrobial therapy proved highly or uniformly fatal At the present time at least one-half of all medical and surgical patients received antimicrobial drugs as a part of their treatment Certainly the advent of these agents represents one of the greatest discoveries of recent years and just as each new discovery in medicine has increased our knowledge and opened up new avenues of approach yet simultaneously imposed new challenges so these agents are no exception to the old adage All is not gold that glitters Their administration has resulted in certain undesirable consequences which constitute new and serious problems in the medical care of patients.

The indiscriminate use of these antimicrobial instruments singly or in combination, has resulted in an increasing number of both drug resistant bacteria and superinfections with endogenous microorganisms which are naturally resistant to these agents in addition to an increasing incidence of untoward reactions to them The spectacular increase in number of antimicrobic compounds resulting from the competitive research efforts of the pharmaceutical industry in its search for more effective and less toxic agents makes it virtually impossible for a busy practitioner to evaluate properly the available antimicrobial remedies Inasmuch as successful treatment with any drug is dependent upon the physician's understanding of the therapeutic agent he pre-

scribes the need is great for a simple guide to the intelligent use of our antimicrobial allies

In this book, we have attempted to crystallize the currently available information regarding the laboratory and clinical applications of the antimicrobial auxiliaries In so doing, we have been prompted by the realization that a great deal of this information, as it is found in our standard textbooks, is often out of date because of the lapse in time required to publish such detailed and comprehensive works

At this time such obstacles as our failure to understand fully the mode of action of these drugs and the mechanism of many of the toxic reactions associated with their use makes such an undertaking difficult. Furthermore the rapid development and introduction of new antimicrobial agents adds to the difficulties of presenting an up-to-date discussion of the subject. Nevertheless a great deal has been learned concerning these drugs and this knowledge can serve as a guide not only for their intelligent use but also as a basis for the evaluation of new drugs as they become available

Success with the antimicrobial agents is dependent upon an early and accurate diagnosis, followed by their *proper* use. This being a discussion of our antimicrobial weapons, we have necessarily stressed the use of these drugs but it is to be remembered that, regardless of their proven therapeutic effectiveness, *they are not to be used to the exclusion or neglect of other proven forms of therapy when such are indicated.*

In the preparation of this work, we have endeavored to present data which accord with the present state of our knowledge and which, though concise, should give to the

student and practicing physician the fundamental principles governing this type of therapy We have tried to indicate what seem to be the important issues and to point out that many conclusions which are generally accepted as final are in reality only provisional and may very probably have to be modified greatly as a result of more accurate observation and more critical consideration of results.

In order to keep the material within reasonable limits we have omitted clinical records and have disregarded for the most part all controversial questions and theories still under discussion Certain references have been inserted in the book for the benefit of those who may wish to study more fully some particular phase of this subject. Those selected to be included refer to contributions which themselves present a more or less complete bibliography dealing with comparatively recent investigations which are either of exceptional importance or historically interesting

Finally we wish to acknowledge the cooperation of those who have contributed in various ways to the preparation of this book. Thanks are due to the Chiefs of Service of the Philadelphia General Hospital (Blockley Division) for affording us clinical facilities and to the House Staff and Nurses for their assistance in the clinical evaluation of these drugs during the past seventeen years To the members of the Department of Laboratories of the Philadelphia General Hospital (Blockley Division) especially Doctors Jefferson H Clark, John G Reinhold and Miss J M O'Loughlin we express our gratitude for their invaluable aid Thanks are due to Dr William W Weiss for his advice concerning the use of these drugs in the treatment of tuberculosis We are also indebted

to certain pharmaceutical manufacturers for providing us with the various antimicrobial agents To the friends of The Research Fund for Infectious Diseases, the Schools of Medi cine, the University of Pennsylvania, we likewise wish to express our appreciation for their financial assistance To the publishers for their cordial cooperation and many helpful suggestions we wish to express our thanks

H F.F
G M.E

Science is the soul of the prosperity of Nations and the living source of all progress — what really leads us forward are a few scientific discover ies and their application. — Louis Pasteur (1822 1895)

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Antimicrobial Agents

SULFONAMIDES

THE chemical treatment of bacterial disease was reopened with the discovery of the effectiveness of the sulfonamide group of drugs in 1935 Since that time, numerous clinical reports have established unquestionably the therapeutic effectiveness of sulfanilamide and its allied compounds in many kinds of infectious disease However the sulfonamides possess definite shortcomings First many strains of bacteria are naturally resistant to their action. Second initially susceptible strains in a species can and do develop resistance to the sulfonamide drugs during treatment, so that a number of bacterial infections are no longer amenable to sulfonamide therapy Furthermore, the antibacterial activity of sulfonamides is diminished in the presence of pus Finally these drugs may produce a variety of serious untoward reactions With the more recent introduction of the antibiotics indications for the sulfonamides have become restricted. Nevertheless, in spite of the superiority of the antibiotics in certain diseases and the known disadvantages of the sulfonamides there still exists a definite place for the latter either singly or combined with the antibiotics in antimicrobial therapy

Mode of Action and Therapeutic Limitations

In order to know the kind of cases in which these drugs are likely to succeed, some knowledge of their mode of action is essential. At this time there are several theoretical conceptions as to the manner in which these drugs act, but no single theory has been evolved which completely explains their action The most widely accepted theory postulates that the action of these drugs is accomplished by interference with essential metabolites *via* a displacement of para aminobenzoic acid from the bacterial enzyme necessary for growth of the organism, since the bacteriostatic action of these drugs has been shown to be prevented by small amounts of para aminobenzoic acid. With this theory it is possible to predict with reasonable accuracy the *in vitro* activities of new sulfonamides Regardless of the exact mechanism of sulfonamide activity certain principles of treatment have evolved as a result of clinical observations of their use in several types of infections It appears that the sulfonamides exert their greatest effectiveness in diffuse lesions characterized by *maximal tissue invasion* and minimal tissue destruction. The presence of necrotic tissue or pus in a lesion prevents the compounds from acting upon the organisms with the same maximum effect which characterizes their action on diffuse nonsuppurative infections. Furthermore if an infection is treated after two or three days of progression, and some degree of localization or pus formation has occurred in the interim, the sulfonamides seem clinically to accomplish little more than to protect uninvolved tissue. Therefore, it is important to start chemotherapy early in the disease process before pus formation takes place because once this has occurred the drugs are *relatively ineffective. Since the introduction of* sulfanil

amide many of its derivatives have received clinical trial. We shall limit this discussion to those in common use. The sulfapyrimidines (sulfadiazine, sulfamerazine and sulfamethazine), sulfisoxazole (Gantrisin, Hoffman La Roche) and sulfisomidine (Elkosin, Ciba) and the relatively insoluble compounds phthalylsulfathiazole (sulfathaladine, Sharp and Dohme) and succinyl sulfathiazole (sulfasuxidine, Sharp and Dohme). In addition the parent substance sulfanilamide is included, although it is seldom used. In general there is little qualitative difference in the antimicrobic spectrum of the various commonly employed sulfonamides. The most susceptible types of organisms include streptococci, staphylococci, pneumococci, gonococci, meningococci, *Escherichia coli*, *H. influenzae*, *Aerobacter aerogenes* and *Proteus vulgaris*. Such compounds as phthalyl sulfathiazole and succinyl sulfathiazole, because of their differences in solubility and absorption, have similar but local action in the gastrointestinal tract. The action of the parent substance sulfanilamide is chiefly against the streptococci and gonococci.

Pharmacology

With the exception of sulfanilamide, the sulfonamides are relatively insoluble in water. However they manifest increased solubility in body fluids. The drug concentrations reached locally and in the blood are dependent upon the rate of entry into, and exit from, the local area and the circulating blood. The rational basis for the local application of the sulfonamides is the higher concentration obtained locally and because of the relatively greater solubility of sulfanilamide in wound fluids, its use locally has proved to be the most satisfactory. However the limitations imposed by the relatively limited solubility of sulfadiazine

and the other sulfonamides in comparison with sulfanilamide, is partially balanced by the fact that the former remain in the wound longer than does the latter When administered by mouth, one may assume for practical purposes that all of these drugs, with the exception of phthalyl sulfathiazole and succinyl sulfathiazole, are nearly completely absorbed from the gastrointestinal tract into the blood stream within from two to four hours after ingestion of moderate doses After four to six hours the amount of drug in the circulating blood diminishes rapidly so that it is important to administer a large initial dose, followed by smaller amounts at four to six hour intervals in order to obtain and maintain therapeutic blood concentrations until complete clinical cures are obtained. Since irregular or varying blood concentrations have been shown to produce diminished therapeutic results the above schedule of doses should be followed if uniformly effective blood levels are to be maintained. Obviously when these drugs are employed parenterally high blood levels are obtained more rapidly than when they are administered locally or by mouth.

Following their absorption into the blood stream, the sulfonamides are partially converted by the liver into the acetyl, or conjugated forms In general, approximately twenty per cent of the drug appears in the circulating blood as acetylated compound. Since these derivatives are therapeutically inactive and tend at the same time to be more toxic, because of diminished solubility a sulfonamide capable of a high degree of acetylation is less desirable than one with a low capacity of this property

For the most part, sulfanilamide and the sulfapyrimidines resemble the behavior of urea in their uniform distribution throughout the body they diffuse readily from the blood

stream into the various body tissues and fluids the pene tration being influenced by the degree of combination with plasma proteins The vascularity of a tissue influences its drug concentration so that diffusion into an area of chronic infection bone and necrotic tissue may be deficient. All of these drugs are present in exudates and transudates in concentrations equal to or higher than those found in the blood They pass readily into the cerebrospinal fluid in concentrations averaging fifty to seventy five per cent of that present in the blood Available data on sulfisoxazole and sulfadimetine indicate that these drugs traverse the hematoencephalic barrier in amounts which result in lower cerebrospinal fluid concentrations than those obtained with other sulfapyrimidines

Regardless of their route of administration the sulfon amide drugs are excreted in the urine to the extent of eighty to ninety per cent of the quantity administered, both in the free and acetylated form For the most part this takes place within twenty four to forty-eight hours. The percentage in the acetylated form varies with the drug and with the patient Sulfonamide excretion is similar to that of urea except that reabsorption by the tubules occurs to a greater extent and elimination is reduced in the pres ence of diminished nitrogen excretion However the clear ance of these drugs is increased definitely by increased urinary flow rate which can be obtained best by forcing fluids either by mouth or if necessary parenterally With a decrease in kidney function one finds an increase in drug concentration in the blood especially the acetylated form. Therefore should the urine volume become low the pos sibility of stone formation in the urinary tract by crystals of the acetyl compounds particularly sulfadiazine sulfa merazine and sulfamethazine, is greatly increased The

possibility of such an occurrence is significantly less with sulfisoxazole and sulfisomidine in view of the greater solu bility especially in acid urine, of the acetylated deriva tives of these drugs

Sulfonamide Mixtures

Although the belief is widely held that administration of sufficient fluid to insure high urinary output is enough to prevent crystalluria and that this hazard is the result of the very low solubility of the acetylated drugs in acid urine, it has been learned that high urine volumes and the use of alkali will not forestall precipitation of sulfadiazine sulfamerazine, or sulfamethazine. However chemical and clinical studies of these agents in combination have demonstrated that the total amount of sulfonamide that can be held in solution in urine is substantially increased when two or more of these substances are administered simul taneously and that this is accomplished without sacrificing therapeutic activity Thus it is possible to lessen the haz ards of urinary tract complications due to sulfonamide crystals or calculi. Hence, the rationale for the combination of sulfadiazine and sulfamerazine with or without sulfa methazine, as a method of decreasing renal toxicity while maintaining antibacterial efficacy Certainly it is still im portant, when using the sulfapyrimidines to maintain a urinary output of at least 1200 cc. (1 1/5 quarts) daily

Toxicology

In discussing the untoward reactions of sulfonamide ther apy it is well to point out several factors which tend to influence their incidence and severity The length of time that the drugs are administered and the total dose employed are probably the most important factors Children

seem to tolerate these drugs better than the aged those with good nutrition and normal renal function better than the poorly nourished and those having kidney damage.

Mild Toxic Reactions

Ambulatory patients complain of dizziness rather commonly especially with sulfanilamide To recognize that dizziness may occur is important especially in the case of patients who operate machines requiring precision or judgment. Cyanosis often observed in patients receiving sulfanilamide is less frequent and less severe with the other drugs of this group and can be disregarded The most frequent toxic reactions seen are nausea and vomiting These usually appear by the first twenty four hours of therapy but rarely become so severe as to necessitate discontinuing therapy

Severe Toxic Reactions

Drug fever is seen in approximately three per cent of patients receiving the sulfonamides It may occur at any time but is most commonly seen from five to ten days after the beginning of treatment. Frequently drug fever may be followed by dermatitis hemolytic anemia, or neutropenia. When it occurs treatment should be stopped. At times it is difficult to determine whether an observed temperature rise represents a drug reaction or a recrudescence of the infection The fever of the original infection is usually normal by the third day of treatment and if the patient is improved clinically one should suspect that the rise in temperature is due to the drug The leukocyte count may or may not be elevated during drug fever As a rule if the drug is causing the temperature it will drop within from twenty four to forty-eight hours following ces

sation of therapy while fluids are forced. If treatment is again necessary it is well to administer 0.3 Gm. (5 grains) of drug by mouth and, if no sharp febrile response occurs within twelve hours, therapy can be reinstituted with extra precautions Drug rashes occur with the sulfonamides in approximately two per cent of patients and may occur at any time after the beginning of treatment, especially after the fifth day If the patient s condition warrants, the drug may be continued with caution, although it is best to stop treatment. Psychoses due to these drugs occur at any time. If the infectious process is under control when psychosis is observed, the drug is best discontinued. Hematuria is not observed with sulfanilamide and rarely with sulfi soxazole and sulfadimetine, but occurs microscopically in about three per cent of patients treated with the other sulfapyrimidines. Likewise, gross hematuria is observed at times following the latter drugs Unless either a consider able number of red cells are detected or evidence of ureteral blockage is apparent, cautious treatment may be continued, but it should be remembered that hematuria is often a precursor of severe renal insufficiency The presence of increasing oliguria or anuria, as well as skin eruption, fever or blood dyscrasia demands immediate alkalization of the urine to a *p*H of 7.5 or more, plus *fluids in order to eliminate* the drug as soon as possible. Bleeding from the urinary tract following the prolonged use of gantrisin may be en countered occasionally Under these conditions, there occurs a lowering of the prothrombin level in the blood. Occasional cases of anuria have been observed during or following the use of sulfadiazine, sulfamerazine and sulfa methazine and in such cases the drug should be stopped immediately In this connection, it should be remembered that renal damage is not always the result of mechanical

stoppage but may consist of a toxic lesion giving rise to tubular degeneration and glomerular changes Depression of the white blood cells may occur at any time, but most cases of agranulocytosis have occurred after twelve days of treatment. Acute hemolytic anemia, seen chiefly following sulfanilamide, may occur following the use of any of the sulfonamides When it appears usually during the first four days of treatment, the drug should be stopped immediately Mild anemia of the hemolytic type is seen more frequently but does not constitute a serious problem. Other toxic effects such as hepatitis nephritis myocarditis purpura hemorrhagica and neuritis may be seen In addition to the above immediate toxic reactions there has been a great deal of interest regarding the possibility that these drugs may give rise to changes in the blood vessels simulating periarteritis nodosa

Methods of Administration and Dosages

The sulfonamide compounds are administered locally orally and parenterally The local use of these drugs has been for the most part disappointing, although they are still being employed in certain specialties In general, their administration by mouth constitutes the most satisfactory method. However in certain instances when a rapid elevation of the drug concentration in the blood is desired, or when oral medication is impractical or impossible, it is necessary to resort to parenteral administration. Sulfanilamide because of its relatively high solubility in water can be given subcutaneously or intravenously as a one per cent solution in sterile physiological saline. Best results with sulfanilamide are obtained *via* the subcutaneous route. For intravenous therapy with the sulfapyrimidines (sulfadiazine sulfamerazine and sulfamethazine) a five per cent

solution of the sodium salt in sterile distilled water is preferred.

Several factors influence the amount of drug required to produce the desired result. As a rule, the dosages are smaller when the compounds are employed prophylactically than when they are used therapeutically Patients treated in bed usually are given larger amounts than those who are ambulatory The type of infecting organism must be considered as to its susceptibility to the drug and also whether the infection is mild or severe Acute conditions, involving soft tissues require different dosages than do chronic bone or urinary tract infections Moreover certain factors such as kidney function, drug absorption, and the state of dehydration all tend to influence the amount of drug found in the blood. From this it becomes apparent that it is impossible to outline a course of sulfonamide therapy which will suit the needs of every patient. Therefore, the following recommendations on dosage are for the treatment of adult patients suffering with acute infections which are severe enough to warrant full sulfonamide dosage.

Sulfonamide Dosage

A blood concentration of free sulfanilamide of 10 mg. per cent will give maximum therapeutic effectiveness in most types of infections caused by susceptible organisms Blood concentrations at this level can be attained by an initial dose of sulfanilamide by mouth of from 3 to 5 Gm. of sulfanilamide followed by doses of 1 0 to 1 3 Gm. every four hours day and night until the temperature has been normal for seventy two hours along with signs of clinical improvement. The dose then is reduced gradually until complete cure is obtained. This dose schedule may be applied in general to the parenteral administration by the subcutaneous route

although the rate of absorption by the tissues will influence the same In general it is necessary to give the drug every six to eight hours in order to maintain adequate blood levels of free drug The dosage of the sulfapyrimidines (sulfa diazine sulfamerazine and sulfamethazine) is essentially the same and although the amount of free drug in the blood is of doubtful significance a concentration of above 5 mg per cent should give maximum results In meningitis higher concentrations about 15 mg per cent are desirable The usual dosage by mouth for these drugs consists of an initial dose of 3 to 4 Gm followed by 1 Gm every four to six hours day and night For intravenous use with the sodium salt the dosage is calculated on the basis of 0 000 Gm per kg of body weight and is repeated at six hour intervals For the most part the dose schedule for the newer sulfonamides (Gantrisin and Elkosin) is somewhat larger than for the sulfapyrimidines especially in urinary tract infections (4 to 6 Gm daily by mouth) For the relatively nonabsorbable sulfonamides (sulfathaladine and sulfasuxidine) the usual dose is 2 Gm every four to six hours orally

Indications

At this time the sulfonamides are indicated in the treat ment of uncomplicated urinary tract infections bacillary dysentery and meningococcic meningitis The use of sul fonamides and antibiotics in combination is of especial value in those infections where it is difficult to obtain sufficient concentrations of any one drug Certainly there has been a renewed interest recently in the use of the sulfonamides particularly in urinary tract infections, largely as a result of the toxic reactions associated with certain of the wide spectrum antibiotics Furthermore such drugs as

sulfathaladine and sulfasuxidine which are poorly absorbed and are largely excreted in the feces are used prophylactically in the preparation of large bowel surgery

Contraindications

The only possible contraindications to sulfonamide treatment is a history of a previous sensitivity to sulfanilamide and its derivatives as manifested by drug fever gross hematuria, dermatitis, hemolytic anemia, neutropenia, or jaundice. Certainly in patients with such a history one should select some other form of therapy such as the antibiotics, rather than run the risk of continuing sulfonamide toxicity In ambulatory patients receiving the sulfonamides, it is best to advise against the use of alcohol, as at times they tend to cause marked dizziness Aside from this there seems to be no evidence that any other form of medication or food is contraindicated.

PENICILLIN

Of the several known penicillins only the benzyl type has achieved extensive clinical acceptance. By virtue of its antibacterial activity negligible toxicity and comparatively low cost, it is the drug of choice for those infectious diseases encountered most frequently Unlike the sulfonamides, penicillin is effective in the presence of pus. With the exception of the staphylococci, no other organisms have been shown to develop a significant degree of *in vivo* resistance to it.

Mode of Action and Therapeutic Limitations

Although the exact mechanism of the action of penicillin is not yet clearly defined, it appears that its maximum action is manifested chiefly against rapidly multiplying

organisms by interfering with their ability to synthesize protein from amino acids, the process being blocked at a point which allows the accumulation of peptides Against susceptible microorganisms its activity may be bactericidal or bacteriostatic, depending upon the concentration at the site of infection Certain species of bacteria, particularly *E coli* are capable of producing an enzyme, penicillinase, which inactivates the drug The organisms most susceptible to penicillin activity are those in the gram positive group Pneumococci, streptococci, staphylococci, certain of the clostridia and strains of lactobacilli. In addition, the gram negative cocci, meningococci and gonococci, are likewise sensitive to this drug Treponemal and borrelial infections including syphilis pinta, yaws and Vincent s angina, can be successfully treated with this drug Penicillin in combination with other antimicrobial agents is likewise a valuable adjunct in the therapy of other diseases

Pharmacology

When administered intramuscularly penicillin is rapidly absorbed into the blood stream. Absorption from the gastrointestinal tract, following oral administration of the crystalline drug is relatively poor The plasma, or serum concentration of penicillin may serve as a rough guide to the amount of drug in the tissues the more important consideration being the amount of penicillin occurring at the focus of infection The amount of penicillin reaching the site of infection is largely dependent upon the rate of absorption into the blood stream the diffusion rate into the tissues, the penicillin binding property of serum proteins the rate of penicillin inactivation at the infected site the diffusion rate from the tissues and the rate of excretion. For the most part, penicillin permeates most tissues except the

brain cornea and lens Obviously in relatively avascular areas such as thick walled abscesses the amount of penicil lin in the tissues is limited. It is possible to obtain effective concentrations of penicillin in the cerebrospinal fluid and vitreous humor by employing massive dosages This is especially so in the presence of acutely inflamed tissues. The need for intrathecal administration is therefore obviated in most cases

Approximately sixty to seventy per cent of parenterally administered penicillin is excreted in the urine the rate of elimination depending on the preparation employed. When given orally approximately twenty per cent is recov ered in the urine Because of the extreme rapidity with which crystalline penicillin is excreted by the renal tubules, it is difficult to maintain high concentrations of the drug in the circulating blood by means of this dosage form Various attempts have been made to prolong the action of the drug either by slowing the rate of absorption from the site of injection, or retarding its rate of elimination. The use of penicillin suspended in peanut oil and beeswax was reasonably successful in prolonging effective concentrations since it constituted a reservoir from which penicillin was slowly given up to the body fluids However because of the occurrence of pain and induration at the site of injection, as well as certain allergic manifestations and sterile abscesses, this method was not found practical. The development of procaine penicillin and other depot penicillins af forded comparable penicillemia with relatively few untoward reactions More recently another penicillin salt, Benzathine Penicillin G (N N[1]-dibenzylethylenediamine dipenicillin G (Bicillin, Wyeth and Co)) has been shown to give plasma penicillin concentrations of greater duration than those reported with any other form of repository penicillin.

Benemid

In order to prevent rapid urinary excretion of penicillin by the renal tubules various renal blocking agents have been employed Thus far the most useful drug for this pur pose is Probeneceid (Benemid Sharp & Dohme Inc.) which has been shown to be capable of producing a two- to four fold enhancement of penicillin plasma concentrations This agent is readily absorbed from the gastrointestinal tract with the development of effective concentrations of the drug within two hours Repeated doses of 0.5 Gm every six hours will maintain effective plasma concentrations of benemid and the slow rate at which the drug is eliminated from the body permits the administration of the drug at intervals spaced as widely as every twelve hours It is proposed that benemid produces its effect by reversibly inhibiting a system of enzymes concerned with the conjugation of certain or ganic acids with glycine and that this system of enzymes is related to the renal excretory mechanism whereby penicillin is excreted. The oral effectiveness of the compound the ability to administer it at widely spaced intervals its seem ing nontoxicity and its ability to elevate by two- to four fold the plasma concentrations of penicillin has made it of real value as an adjunct to the therapy of resistant infections amenable to intensive penicillin therapy In addition bene mid offers considerable promise of increasing the usefulness of oral penicillin. When this compound is incorporated into oral penicillin it is possible to produce sustained therapeutic levels in the blood with a tablet containing 300 000 units of penicillin and 0 75 Gm. of benemid taken every eight hours

Benzathine Penicillin G (DBED)

The development of Benzathine Penicillin G (N N[1] dibenzylethylenediamine dipenicillin G (Bicillin Wyeth

and Co and Permaden, Chas Pfizer and Co) represents an important advance in antibiotic therapy in that it elim inates oil, beeswax, and aluminum monostearate, which were formerly necessary to obtain prolonged penicillin action Following a single intramuscular injection of 1,200 000 units therapeutic plasma penicillin levels were detected twenty four days later Although the peak plasma concentration with this penicillin salt is low it is adequate for many pneu mococcal and streptococcal infections as well as for syphilis and gonorrhea. Furthermore, Benzathine Penicillin G being an insoluble salt and hence tasteless, has been widely used orally in an aqueous solution. At this time, its chief usefulness has been its prophylactic properties especially against hemolytic streptococcus infection of the throat and in patients suffering with chronic bronchopulmonary diseases to prevent bacterial flare-ups In addition, it is employed successfully in the treatment of certain forms of syphilis

Penthemate

The concept of penicillin derivatives having affinity for certain tissues or organs of the body is not new but not until recently has there been a penicillin preparation pos sessing this property to a degree that is therapeutically sig nificant. In 1948 in a general search for a repository form of penicillin salt, penthemate (the diethylaminoethyl ester of penicillin G) was prepared as a hydriodide (Neo-penil, Smith, Kline & French Laboratories) When the compound was found to have the unique property of marked diffusibil ity into the pulmonary and brain tissues of guinea pigs, it naturally suggested obvious therapeutic advantages Fur ther studies in cats and dogs confirmed the original obser vations of higher penicillin concentrations in lungs and

brains of guinea pigs following Neo-penil than those after procaine penicillin G

Animal and human experiments have shown that Neo-penil has a far greater affinity for the lungs than have the other penicillin preparations Since these unusually high tissue concentrations occur in the absence of high blood levels it is felt that the tissue concentrations are due to the phar macological property of the drug, rather than to a high blood tissue diffusion gradient. Furthermore, it has been shown that Neo-penil is a repository penicillin but to a lesser degree than is procaine penicillin The lower penicillin plasma concentrations following Neo-penil are reflected in smaller urinary recoveries (thirty-one per cent) as compared to sixty two per cent for procaine penicillin This smaller urinary recovery following the intramuscular administration of Neo-penil can be interpreted in various ways (1) The elimination of the antibiotic by excretory pathways other than the urinary tract, or (2) destruction of the material in the tissues of the body According to several groups of investigators significant quantities of penicillin are excreted in the saliva and bronchial secretions clearly demonstrating that the drug is eliminated from the body by ways other than the kidneys The likelihood of significant quantities of Neo-penil being sequestered in the tissues of the body and being released slowly seems doubtful, since the urinary ex cretion of penicillin approaches the limit of measurability by the end of twenty four hours. It has also been demon strated that Neo-penil produces penicillin spinal fluid con centrations about ten times greater than those produced by equal doses of procaine penicillin G or potassium penicillin G in the same patients Furthermore in patients studied at the time of delivery it was found that Neo-penil furnishes

higher penicillin concentrations to the fetus than procaine penicillin G

Clinical studies have indicated that Neo-penil is superior to other penicillin preparations in the management of some types of chronic pulmonary infections, such as bronchitis, bronchiectasis and chronic pneumonitis These clinical results were mostly evident in the relief of cough, the decrease and change in the character of expectoration, and the control of temperature Neo-penil has also been shown to be equally as effective as procaine penicillin in the treatment of acute pulmonary diseases such as bacterial pneumonias Thus far clinical material dealing with the treatment of meningeal infections is limited, but in several cases of meningococcal meningitis results have been satisfactory In addition Neo-penil may prove therapeutically valuable in syphilis and gonorrhea of pregnancy Prophylactically it may be important in the treatment of patients with prolonged rupture of the membranes There is reason to believe that Neo-penil may have special usefulness in the treatment of certain types of infections involving the lymph nodes Despite these apparent advantages acceptability of Neo-penil as a clinically valuable drug is diminishing because of the acute anaphylactoid reactions attendant upon its use.

Oral Penicillin

A preference for the oral over the parenteral route of administration for any medication is freely acknowledged when the two routes have equal therapeutic effect. The restricted supply of penicillin at the time it was first employed makes it understandable that all the possibilities of oral penicillin therapy were not explored. However the almost unlimited supply of penicillin available within recent

years has encouraged investigation of these possibilities and it has been shown that if large enough doses are given by mouth, this route of penicillin administration produces adequate results. Not only is the oral route more convenient, but also it is least apt to cause toxic reactions A variety of salts of oral penicillin have been studied and none is superior to potassium penicillin G in height or duration of blood levels obtained. When penicillin is administered orally the dosage should be three to five times that by intramuscular injection. However the oral route should not be used in overwhelming infections in localized suppurations in which diffusion of penicillin is poor or in the presence of nausea, vomiting, or other gastrointestinal disturbances

Hypoallergic Penicillins

There are several hypoallergic penicillin compounds now available, allylmercaptomethyl penicillin (Cer-O-Cillin Upjohn & Co) and L-ephenamine penicillin (Compenamine Commercial Solvents Co) to which according to some investigators the incidence of sensitivity reactions is lower than with penicillin G In an occasional case such as subacute bacterial endocarditis it may be necessary to try one of the hypoallergic penicillins However in most circumstances it would appear expedient to substitute another antibiotic or to employ an antihistaminic drug or attempt to desensitize the individual to penicillin G

Topical Applications

In addition to the parenteral and oral preparations penicillin is available for local use in such forms as nose drops dusting powder sublingual tablets troches and ointments Penicillin is also available for aerosol therapy

Toxicology

The chief untoward reactions to penicillin therapy fall into three principal groups (1) Local contact (skin, mucous membranes, and injection site) (2) dermatological allergy (urticarial, erythematous and eczematoid) (3) systemic (serum sickness anaphylactoid, cardiovascular and renal) In addition, there have occurred certain specific phenomena associated with some particular disease being treated with penicillin, such as the Herxheimer reaction in syphilis and the development of a Loeffler s syndrome following aerosol penicillin in the treatment of some types of pulmonary dis ease. Furthermore, evidence is pointing towards penicillin as giving rise to a variety of disorders including agranulocytosis periarteritis nodosa, the production of L. E. cells in the bone marrow and others

At the time that penicillin was first made available for general civilian use, it was not known how many of the described toxic reactions were due to impurities in the penicillin preparations or to the drug itself. Probably the total inci dence of penicillin reactions was decreased because of the in creased purity of the drug. However the total number of reactions has increased steadily and today penicillin heads the list of medicinal agents in frequency diversity and severity of the sensitivities it produces No doubt this is a result of the fact that the drug is used promiscuously and repeated administration of it to ever increasing numbers of people has resulted in their being conditioned to show various manifesta tions of hypersensitivity when exposed to subsequent penicillin therapy Rarely does a patient experience a reaction after the first dose of penicillin, whereas the reactions become more frequent and more severe in individuals who have had repeated doses. Some of the reactions occurring after the

first dose are believed to be related to cross reactions with other fungi, particularly trichophytosis (athlete s foot) The more serious reactions, such as anaphylactic shock occur most often in patients with allergic histories especially asthma. Although any penicillin preparation and any mode of administration can cause a reaction, it appears that oral penicillin is the least likely parenteral preparations next in frequency and topical penicillin the most likely to cause reactions Reports of acute anaphylactoid reactions due to penicillin are being reported with increasing frequency with most of the severe cases following the intramuscular ad ministration of procaine penicillin or Neo-penil, with a higher incidence after the latter drug This may be due to a greater amount of sensitizing substance that is present longer the possible synergistic effect when two substances are injected simultaneously or as in the case of Neo-penil, one must consider the possibility of iodide sensitivity

In spite of the foregoing penicillin remains the least toxic of the currently available antimicrobial agents. Its well established therapeutic value and relatively lower cost com bine to establish it as the most popular drug Hence, every effort should be made to minimize the reactions following its administration. A history of previous penicillin toxicity should, in most cases contraindicate the use of penicillin and manifest the desirability of administering another anti biotic, if possible However many patients can tolerate peni cillin even after a previous allergic reaction and in such conditions as subacute bacterial endocarditis in which peni cillin is strongly indicated, one may proceed with caution When reactions do occur and are not too severe, treatment can usually be continued with the aid of antiallergic reme dies Obviously the more serious reactions demand dis- continuance of the drug Such reactions as anaphylactoid

shock and exfoliative dermatitis demand prompt attention and treatment with supportive measures epinephrine, anti histaminics and intravenous ACTH The advisability of routinely using a penicillin product in which an antihistaminic agent is included can be questioned, in that one is adding another potentially toxic agent. However the concomitant use of an antihistaminic is indicated in patients with allergic histories especially asthma. Where possible, oral penicillin should be used in preference to the parenteral route Intra muscular injections must be given with caution, as it has been implied that some of the severe, or fatal, reactions are the result of the accidental intravenous injection of procaine penicillin, or Neo-penil. Topical application in the form of troches toothpaste aerosol, ointments and dusting powders is of doubtful value in most instances and should be discouraged. Certainly penicillin therapy should be reserved for infections which are amenable to its action and with held in trivial illnesses and conditions where its effectiveness is not established. Furthermore, penicillin should not be used prophylactically except when the complication to be avoided is a serious one and occurs frequently in the absence of precautions

Some investigators rely on skin testing as a guide in determining possible penicillin sensitivity but as yet there seems no complete agreement as to the value and signif icance of skin test results A possible exception is the significance of the immediate whealing reaction on cutaneous or intracutaneous testing as regards the development of an anaphylactoid reaction

Efforts to desensitize patients who have experienced peni cillin reactions have been considered successful in the hands of some experienced workers This procedure may be tried, especially when the patient's occupation, *e g.*, nursing,

necessitates exposure to the drug or in conditions where penicillin is urgently needed If the sensitivity reaction has been severe, an initial dose of two units of aqueous penicillin G is given intramuscularly other cases are given 50 units every three hours the first twenty four hours 100 units every three hours the second forty-eight hours with the dose being doubled each twenty four hours until the patient can tolerate 200 000 units.

Dosage

Although a concentration of 0 03 units per cc. of plasma or serum has been considered as a minimum effective therapeutic level and is effective in many types of infections one may enjoy a false sense of security in relying on this concentration for the treatment of every type of infection susceptible to penicillin On the other hand when treating infections where the etiologic agent is extremely sensitive to penicillin *e g* pneumococci gonococci and the treponemas of syphilis, this concentration may actually be higher than is needed. The clinical importance of penicillin plasma concentration measurements has been called into question indeed there are some who contend that they have no significance There is evidence to indicate that tissue concentration of penicillin may actually be higher than that existing in the circulating blood and that significant amounts of penicillin are excreted in the urine long after the amounts in the blood have fallen below a detectable level. Such observations do not necessarily vitiate the practical value of plasma concentration determinations so long as it is remembered that the amounts of penicillin measured in the plasma are only an indirect, rough gauge of the amount of penicillin being delivered at the actual focus of infection The fact seems to be that many infections are so susceptible to peni

cillin therapy that quite frequently little attention need be paid to the penicillin plasma concentrations because any of the usual dosage schedules will effectively control the infection. Only in the treatment of more resistant infections can the significance of penicillin plasma concentrations be more clearly interpreted in terms of its relationship to therapeutic effect.

The effectiveness of plasma concentrations of penicillin following any given dose, is dependent largely upon the *specific susceptibility of the organism being attacked.* The type of activity resulting from a given concentration might fall into one of several kinds the activity may be bactericidal, actually destroying the organisms bacteriostatic, preventing increase in numbers of the organisms or both. Maintenance of bacteriostasis for a prolonged interval of time ultimately results in destruction of the bacteria by senescence or starvation. The duration of penicillin action which produces bactericidal, or bacteriostatic, or both effects simultaneously might well be designated as the "total penicillin effect time" upon the organism under treatment. In this connection, it would seem that the best way to achieve and maintain optimally bactericidal concentrations for an appreciable length of time would be to administer *penicillin by continuous infusion, thereby compensating for* the rapidity of its renal excretion It is to be remembered, however that for penicillin to be bactericidal, not only must the drug concentration be optimal, but also the susceptible organisms are required to be in a state of active multiplication Continuous maintenance of the lethal concentration *may suffice only to check the organisms undergoing active* fission, but fail to kill those organisms which are present in a physiologically inactive phase. These so-called resting organisms or persisters may become vulnerable to the ac-

tion of penicillin only if they are permitted to resume multiplication. It is also of interest that therapy of an intensity which yields a continuous bacteriostatic effect is attended by antibody formation which is diminished in comparison with that associated with intermittent therapy In the latter case opportunity is afforded for some multiplication of the surviving bacterial population From the foregoing it is natural to inquire whether it is more desirable to achieve bactericidal levels of penicillin intermittently or continually to maintain concentrations that approximate the bactericidal range At this time clinical reports indicate that in most serious infections it is best to employ intermittent therapy rather than continuous infusion. However excellent results have been obtained with the latter route Today the confusion concerning penicillin administration is in considerable measure attributable to the variety of preparations available. The relative advantages of the most commonly employed dosage forms may be summarized as follows

1. *Crystalline benzyl penicillin in aqueous solution* administered intramuscularly 100 000 units.
   Peak plasma concentration 1.0-3.0 units.
   Time after administration: Fifteen to thirty minutes.
   Total duration of therapeutic plasma concentration: Three hours.
   Recommended interval for injections (depending on type and severity of infection): Three to twelve hours.
   Advantages: Lowest cost per dose most rapid action, maximum peak concentration with consequent greatest diffusion into serious cavities and abscesses, shortest duration of toxic reactions
   Disadvantages: Necessity for frequent (two to three daily) injections, inconvenient at home
2. *Procaine penicillin with sodium carboxymethyl-cellulose prepared for aqueous suspension* 800 000 units administered intramuscularly
   Peak plasma concentration: 1.0 units.
   Time after administration Two hours.

Total duration of therapeutic plasma concentration Twenty four hours.

Recommended frequency of doses (depending on type and severity of infection) Twelve to twenty four hours.

Advantages Requires only a single daily injection for most infections. Most economical preparation for routine hospital use.

Disadvantages High plasma concentrations are not obtained even with frequently repeated doses

3. *Procaine penicillin with aluminum monostearate in oil*, intramuscular administration 300 000 units

Peak plasma concentration 0 5 unit.

Time after administration One hour

Total duration of therapeutic plasma concentration Forty-eight hours (in most instances ninety-six hours)

Recommended frequency of doses (depending upon the type and severity of the infection) Forty-eight hours.

Advantages Most convenient preparation for home administration.

Disadvantages Toxic and allergic reactions to penicillin, procaine or oil, although rare are of extended duration.

4 *Neo-penil in aqueous suspension (hydriodide of diethylaminoethyl ester of penicillin G)* 500 000 units administered intramuscularly

Peak plasma concentration 1 0 unit.

Time after administration Two hours.

Total duration of therapeutic plasma concentration Twenty four hours.

Recommended frequency of doses (depending upon type and severity of infection) Twelve to twenty four hours.

Advantages Requires only a single daily injection for most cases. Especially recommended for chronic lung conditions.

Disadvantages High plasma levels are not obtained even with frequently repeated doses. Higher incidence of anaphylactoid reactions.

5 *Benzathine Penicillin G (N N^1-dibenzylethylenediamine dipenicillin G)* intramuscular administration, 600 000 units.

Peak plasma concentration 0.20 units.

Time after administration Three hours.

Total duration of therapeutic blood concentration Ten days. Twenty four days (1,200 000 units)

Recommended frequency of doses Ten to twenty four days.

Advantages Requires only a single monthly injection for prophylactic usage.
Disadvantages Possible prolonged toxicity

6. *Penicillin buffered* oral tablets 200 000 units.
Peak plasma concentration 0 4 units.
Time after administration Thirty minutes.
Total duration of therapeutic plasma concentration Three hours.
Recommended frequency of doses (depending on type and severity of infection) Three to six hours.
Advantages Ease of administration especially at home
Disadvantages Greater cost.

Certainly the characteristics of the various preparations provide advantages for specific purposes The use of procaine penicillin in aqueous solution once daily is less expensive than aqueous crystalline penicillin given at three to four hour intervals and is adequate for most infections. When treating such infections as meningitis or endocarditis however the low level concentrations afforded by depot or oral penicillins will not provide sufficient diffusion and frequent intramuscular administration of aqueous crystalline penicillin is indicated. Prophylactically the advantage of benzathine penicillin G which provides effective levels for two to three weeks is of definite value

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

Streptomycin and dihydrostreptomycin remain uniquely valuable for the treatment of tuberculosis and should, for the most part, be reserved for this purpose Certainly the development of the wide spectrum antibiotics has to a significant degree diminished the importance of these two therapeutic agents in other infections.

Mode of Action and Therapeutic Limitations

Streptomycin and dihydrostreptomycin organic bases are essentially bacteriostatic for growing cells but under ap-

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3 *Procaine penicillin with aluminum monostearate in oil,* intramuscular administration 300 000 units.

Peak plasma concentration 0.5 unit.

Time after administration One hour

Total duration of therapeutic plasma concentration Forty-eight hours (in most instances ninety-six hours)

Recommended frequency of doses (depending upon the type and severity of the infection) Forty-eight hours.

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Disadvantages Toxic and allergic reactions to penicillin, procaine or oil, although rare, are of extended duration.

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Peak plasma concentration 1 0 unit.

Time after administration Two hours.

Total duration of therapeutic plasma concentration: Twenty four hours.

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Mode of Action and Therapeutic Limitations

Streptomycin and dihydrostreptomycin organic bases are essentially bacteriostatic for growing cells but under ap-

propriate conditions may also be bactericidal. Their effectiveness is increased in alkaline media. Like penicillin, these agents are most effective against multiplying bacteria, but, unlike penicillin, they may have some activity against resting cells. The mechanism by which these drugs produce their antibacterial effects is postulated to be an interference with the oxaloacetate-pyruvate condensation mechanism. A distinct disadvantage to the use of streptomycin and dihydrostreptomycin is the frequency and rapidity with which susceptible bacteria develop resistance to these agents. While resistance to penicillin develops gradually after many exposures, resistance to streptomycin and dihydrostreptomycin may range from slight to almost absolute following a single exposure. These drugs are effective as adjuncts in the treatment of tuberculosis and are of definite value in the treatment of urinary tract infections, bacteremia, wound infections due to gram negative organisms and tularemia

Pharmacology

When administered by mouth, streptomycin and dihydrostreptomycin are not absorbed from the gastrointestinal tract and little or no drug is found in the blood. However they are not destroyed in the gastrointestinal tract and hence exert activity on the intestinal flora. When given intramuscularly or subcutaneously therapeutic blood concentrations of the two substances are rapidly obtained. Following an 0.5 Gm. dose parenterally blood concentrations, the effectiveness of which will depend on the nature of the infection, will be established and maintained for approximately six to twelve hours About fifty per cent of the administered dose is recovered in the urine within twenty-four hours. The drugs penetrate the peritoneal cavity following parenteral administration, but do not reach empyema cav

ities or spinal fluid except in the presence of inflamed men inges in therapeutic amounts They are concentrated and excreted in the bile.

Toxicology

In general, the severity of toxicity from both streptomy cin and dihydrostreptomycin is dependent upon the dura tion of therapy and total dose employed, the principal toxic effect being damage to the 8th nerve and vestibular apparatus While this is particularly true of streptomycin there seems to be a lesser tendency of dihydrostreptomycin to affect the vestibular apparatus However damage to the auditory branch of the 8th nerve with consequent hearing loss may occur following dihydrostreptomycin Since pa tients are able to compensate for damage to the vestibular but not auditory branch, it is obvious that dihydrostreptomycin is less desirable than is streptomycin especially for long term therapy such as is necessary in tuberculosis. Oc casionally dihydrostreptomycin is useful in patients who are allergic to streptomycin as sometimes allergies do not develop in patients receiving this drug whereas were they receiving streptomycin allergies would develop The recent practice of employing mixtures of streptomycin and dihy drostreptomycin has markedly reduced the toxic effect frequently associated with the individual drugs Either of these compounds may give rise to a variety of less severe reactions, including the sensitivity reactions encountered with penicillin.

Methods of Administration

Both streptomycin and dihydrostreptomycin are given in tramuscularly orally or locally When administered systemically for infections other than tuberculosis the average

daily dose is 1 to 2 Gm with the total dosage depending on the severity of the infection and the sensitivity of the infecting organism. Larger doses 4 to 8 Gm are employed for oral administration. When used intrathecally 20 mg. of dihydrostreptomycin dissolved in 10 cc. of isotonic salt solution is employed, the daily dose not exceeding 50 to 75 mg. Solutions containing 0.5 mg per cc may be used in the treatment of eye and wound infections

THE TETRACYCLINES

Chlortetracycline, Oxytetracycline, Tetracycline

From the beginning of their clinical use aureomycin and terramycin have had much in common, being therapeutically effective in many of the same diseases in the same doses having similar toxic reactions and inducing the emergence of resistant organisms especially the staphylococci. The close relationship between these two drugs became more apparent with the announcement in 1952 of their molecular structures the only difference being that aureomycin has an organic chlorine atom and terramycin a hydroxyl group attached to the tetracycline structure. Thus the chemical descriptive terms, chlortetracycline (Aureomycin, Lederle Laboratories) and oxytetracycline (Terramycin, Chas Pfizer & Co., Inc.) were designated in 1953 for the two drugs respectively In search of better antimicrobial agents, chlortetracycline and oxytetracycline have been divested chemically of their differentiating constituent groups and a new antibiotic agent, tetracycline (Achromycin, Lederle Laboratories Tetracyn, Chas Pfizer & Co Inc. Polycycline Bristol Laboratories and Steclin, E. R. Squibb & Sons) was developed It has also been reported that tetracycline has been obtained by direct fermentation

with the use of an organism originally isolated from a sample of soil from Texas

Mode of Action and Therapeutic Limitations

Chlortetracycline, oxytetracycline and tetracycline are either bacteriostatic or bactericidal *in vitro* depending upon concentration Little is known regarding the exact mechanisms whereby they produce their effects The antibiotics are effective against some of the larger viruses rickettsiae both gram negative and gram positive bacteria including penicillin resistant, streptomycin resistant, and streptomycin-dependent organisms Used in combination with other antibiotics, they are of value in the treatment of certain infections *In vitro* studies have shown that many organisms developing resistance to one of these agents, simultaneously become refractory to the activity of the others which is probably explicable on the basis of close similarity in their chemical structure. However this cross resistance pattern is not an absolute one. Oddly enough, bacteria which develop this cross resistance may often show an increased susceptibility to streptomycin

Pharmacology

Chlortetracycline oxytetracycline, and tetracycline are rapidly absorbed from the gastrointestinal tract within two to four hours and effective therapeutic concentrations are maintained for relatively long periods of time (six to eight hours) following a moderate dose (0.5 Gm) Relatively large amounts are recovered from the urine within twelve to eighteen hours. Although these agents are found in the peritoneal fluid spinal fluid, and bile there seems to be a lack of agreement as to the actual concentrations obtained.

Toxicology

Chlortetracycline oxytetracycline, and tetracycline frequently give rise to gastrointestinal and genitourinary disorders (nausea, vomiting, diarrhea, stomatitis, vaginitis, and proctitis) While these are not usually serious they do cause considerable inconvenience and at times become quite severe In our experience to date tetracycline appears to be least offensive in this manner It is felt that these untoward reactions are due at least in part, to altera tion in bacterial flora leading to a vitamin B deficiency There is evidence to support the view that chlortetracycline stimulates the growth of some types of fungi, notably *Candida albicans* and that these two factors combine to produce a moniliasis When these drugs are used for periods exceeding seven days the patient should receive buttermilk, vitamin B complex, and B_{12} orally if toxicity develops the drugs should be discontinued, if possible and injections of crude liver or B_{12} given daily The use of rectal suppositories containing sodium lauryl sulfate is at times beneficial.

Methods of Administration and Dosages

For the most part, the dosages of chlortetracycline, oxy tetracycline and tetracycline are similar When given by mouth, the usual initial dose of 0.5 to 1 Gm. is followed by 0.25 to 0.5 Gm. every four to six hours depending on the severity of the infection and the response of the patient. Parenteral preparations of these drugs are available and are useful in special conditions. In addition, they are available in the forms of ointments troches, powders, and solutions for local use. Unlike penicillin and streptomycin, which may be bacteriostatic or bactericidal in concentrations at

tainable in the tissues, chlortetracycline, oxytetracycline and tetracycline are only bacteriostatic under similar conditions As a consequence, it is necessary to administer these agents for a greater number of days after defervescence than is the case with penicillin and streptomycin.

CHLORAMPHENICOL

Chloramphenicol (Chloromycetin, Parke-Davis Co) has almost the same range of activity as the tetracycline group as well as the same toxic reactions, although a few individual differences in behavior and toxicity do exist. Best known *is the strikingly greater effectiveness of chloramphenicol in* typhoid fever as well as its possible toxic effect upon the hemopoietic system Despite this potential toxicity chloramphenicol remains a valuable drug for many other infections which fail to respond to other forms of therapy Furthermore, some organisms developing resistance to the tetracycline group simultaneously become refractory to chloramphenicol. In general, the dosage and routes of administration are the same with chloramphenicol as with the tetracyclines although the total daily dose is often larger (1 to 4 Gm)

ERYTHROMYCIN

Erythromycin (Ilotycin Eli Lilly Co Erythrocin Abbott Laboratories) has been shown to possess bacteriostatic activity chiefly against the gram positive organisms One of the chief advantages of this preparation is its effectiveness against penicillin resistant staphylococci and streptococci. At the time this agent first became available *in vitro* testing in the authors laboratories as well as in others rarely revealed any organism of these types to be resistant to attainable serum concentrations of this drug However *in vitro*

studies have demonstrated that such cocci can be "trained to become resistant by culturing in increasing concentrations of the drug. Further with increasing clinical usage, the incidence of erythromycin resistant staphylococci occurring in patients appears to be increasing Erythromycin has shown *in vitro* activity against the Neisseria, Hemophilus, and Brucella organisms as well as an antituberculosis effect. Rickettsiae Spirochetes and *Endomoeba histolytica* also appear to be affected adversely When administered by mouth, a significant portion of the activity is destroyed by the gastric acidity a condition which has been remedied by preparation of especially coated tablets With these, it has been possible to demonstrate fairly good absorption from the intestinal tract. Detectable concentrations have been found in the blood, urine, feces, and cerebrospinal fluid of the experimental dog after oral administration. It has been detected in the serum, cerebrospinal fluid, pleural fluid, and bile after oral administration in man Dosages of 100 to 200 mg every four to six hours by mouth have been recommended although doses up to 1 Gm. have been tolerated. Intravenous dosage is 250 mg every six to eight hours

It appears to be of relatively low toxicity and the only undesirable effect noted in many patients treated with this drug has been an occasional gastrointestinal upset with high dosage. It does not appear to have an adverse effect on the ecology of the gastrointestinal flora, hence, some of the symptoms of the antibiogenic syndrome are thus avoided.

CARBOMYCIN

The activity of carbomycin (Magnamycin, Chas. Pfizer & Co Inc.) is directed against the gram positive organisms the Neisseria, the Hemophilus group rickettsiae, large viruses and certain protozoa. It appears to be effective *in*

vitro against some of the staphylococci resistant to penicillin, thus providing another weapon against the rising problem of resistant organisms. In general, however magnamycin has yielded disappointing clinical results and cannot at this time be recommended as a useful antibiotic for general use. This may be partially explained by the fact that carbomycin is composed of carbomycin A (ninety per cent) and carbomycin B (ten per cent) and, according to studies in our laboratory the A fraction does not diffuse readily into body tissues and fluids whereas the B fraction does Tests are under way evaluate the clinical effectiveness of the latter but it is too early to assess its therapeutic value.

Magnamycin substance can be administered orally intravenously or intramuscularly although the latter route has been reported to cause some discomfort. Experimental studies suggest that following absorption the drug is widely distributed, but that rapidly disappearing serum concentrations may be evidence of deposition in such organs as the spleen liver kidney heart, and lung. The recommended dosage of 2.0 Gm. per day in four to six divided doses has infrequently been accompanied with mild gastrointestinal upsets No other evidence suggesting toxicity has been described.

POLYMYXIN

Although polymyxin B sulfate (Aerosporin, Burroughs Wellcome & Co Inc) is an agent of moderate toxicity (renal and central nervous system) its unique effectiveness in infections due to *Pseudomonas aeruginosa* has justified its introduction into clinical practice Polymyxin B is one of five chemically distinct, but related agents all of which are basic polypeptides possessing a unique activity against gram negative bacilli It is generally felt that this drug is

rapidly bactericidal against multiplying cells, although there is some difference of opinion regarding its behavior toward resting cells Observations of emergence of resistance to polymyxin are unusually rare This antibiotic should be employed parenterally only in hospitalized patients since careful observation for renal damage is essential to its safe use. Its intramuscular use (2.5 mg per kg body weight in diluted doses every four to eight hours not to exceed 200 mg. daily) is justified for the serious and increasingly frequent instances of pyelonephritis, septicemia, or meningitis due to pseudomonas. The dosage for intrathecal use is 5 mg. per day for three days or less then an equal amount on alternate days Infections with some strains of pseudomonas may be susceptible to streptomycin or one of the wide-spectrum antibiotics if the infection fails to respond to these agents a trial of polymyxin B appears justified. Oral or topical preparations of this agent, alone or in combination with other antibiotics are undoubtedly valuable for the treatment of gastrointestinal disease in which the infection is confined to the intestines and for ulcers decubiti, and similar lesions caused by gram negative bacilli which are accessible for local application Furthermore polymyxin B is employed prophylactically in intestinal surgery

BACITRACIN

Since the parenteral administration of bacitracin is often followed by kidney damage and, only a small amount is absorbed when given by mouth, this drug finds its chief usefulness as a topical or oral medicament. For the most part, it exerts its greatest activity against the gram positive organisms as it has little or no activity against the gram-negative types with the exception of meningococci, gono-

cocci, and *Hemophilus influenzae* The oral dosage is 10 000 to 100 000 units daily in divided amounts When administered locally in the form of ointment or solution 500 units per gram or cc. are used. For intramuscular administration dissolve the contents of each vial (50 000 units) in 5 cc. of water Dosages should be limited to 10 000 units every six to eight hours but may be increased two-fold if the situation is critical. Since the incidence of toxic reactions increases significantly at high dosage levels the total daily dose should not exceed 100 000 units For intrathecal administration concentrations of 1000 units/cc are satisfactory The drug is especially useful for the treatment of postoperative wound infections due to penicillin resistant staphylococci

NEOMYCIN

Neomycin displays activity against gram positive acid fast, and gram negative bacteria When administered systemically this drug may cause slight to severe deafness as well as transient renal irritation. Since neomycin is not absorbed into the circulating blood stream from the gastrointestinal tract or skin it has found its chief usefulness in preoperative preparation for intestinal surgery and as a topical medicament for pyogenic skin infections Neomycin, orally 1 Gm every 4 hours is the usual dosage Ointments containing 5 mg of neomycin per Gm of petrolatum lanolin base or wet compresses with 3 to 5 mg of neomycin per 3 ml. are effective in many types of skin lesions Neomycin may be administered intramuscularly 1 Gm every six to eight hours for short periods of time, especially in Proteus and Pseudomonas infections involving the urinary tract.

PARA AMINOSALICYLIC ACID

Para aminosalicylic acid has been shown to possess weak but definite tuberculostatic activity and is effectively employed concomitantly with streptomycin to retard the devel opment of resistance to streptomycin. While the tuberculostatic activity of PAS has been shown to be prevented by para-aminobenzoic acid, it is as yet unknown what role if any this mechanism exerts in development of resistance Except for nausea anorexia, and diarrhea, there have been few untoward reactions accompanying its use. PAS is usu ally given by mouth, 10 to 12 Gm. daily It may also be given intravenously in which case the sodium salt is preferred because of its solubility More recently a combina tion of this agent with polyvinyl pyrrilidone has been reported as producing higher concentrations of PAS which are maintained for longer intervals of time than an equiv alent dosage of PAS in aqueous solution.

ISONIAZID

The hydrazide of isonicotinic acid had been synthesized by Austrian chemists more than thirty years ago but had not been studied from the standpoint of antimicrobial ac tivity Several groups of investigators in this country and Europe, had undertaken a search for thiosemicarbazones that were less toxic than tibione Remarkably three dif ferent laboratories independently and almost simultaneously observed that isonicotinic acid hydrazide had a very high degree of antituberculous activity both *in vitro* and in ex perimentally infected animals.

Dramatically and prematurely announcement was made through the press in 1952 of a new chemotherapeutic agent effective in tuberculosis The original description of as tonishing weight gain, disappearance of toxemia, and fail ure of development of drug resistance appeared to herald

a radical change in the treatment of tuberculosis. Subsequent experience with isonicotinic acid hydrazide now designated isoniazid required considerable modification of the original claims It was shown that tubercle bacilli became resistant to the drug within a few weeks and clinical improvement was not long maintained When combined therapy with isoniazid and streptomycin was employed, however the emergence of drug resistant strains was retarded and a prolonged effect of the isoniazid could be demonstrated It now appears that isoniazid should never be used alone in the treatment of tuberculosis, but that in combination with streptomycin it may prove to be the most effective regimen of chemotherapy yet developed for treatment of pulmonary and extrapulmonary tuberculosis From a practical standpoint, isoniazid has two advantages over PAS in that oral dosage is smaller and more easily tolerated and the cost on a daily dosage basis is less Attention is now being concentrated on the question of whether PAS should be used in conjunction with the other two drugs

Controlled clinical studies have been reported which indicate the value of isoniazid in pulmonary tuberculosis as well as in a wide variety of forms of extrapulmonary tuberculosis Application of isoniazid to the treatment of miliary and meningeal tuberculosis has given encouraging results, which may eventually prove superior to those obtained by use of streptomycin and PAS

The administration of isoniazid may be followed by a variety of untoward reactions the severity of which depends on the dosage length of administration, renal function and personality stability Such symptoms as increased reflexes headache muscular twitchings peripheral neuropathy euphoria, excitability constipation vertigo dryness of mouth and visual difficulties are the principal toxic side-effects encountered. Cessation or decrease, in therapy

is dependent on the type and severity of the reaction. Recently the use of pyridoxine hydrochloride has been shown to be effective in relieving pain in cases with peripheral neuropathy

NITROFURANTOIN

The antimicrobial activity of the nitrofurans has been known since 1944 and furacin has been used widely as a topical antibacterial agent. More recently nitrofurantoin (Furadantin Eaton Laboratories) has been shown to have properties valuable in the treatment of urinary tract infections Although it is contended that forty five per cent of an orally administered dose is excreted in the urine, blood levels are extremely low and the high solubility makes crystalluria infrequent. The antibacterial spectrum of nitrofurantoin *in vitro* includes both gram positive and gram-negative organisms. It is bacteriostatic and may be bactericidal to most strains of staphylococci, *E coli*, *Streptococcus pyogenes* and *A. aerogenes* it is less effective against Proteus and ineffective against *Pseudomonas aeruginosa*. Resistance to nitrofurantoin did not develop readily *in vitro* This drug has been well tolerated when given orally in daily dosage of 5 to 8 mg per kg. of body weight, in four divided doses with meals and with a bedtime snack. Larger doses result in nausea and vomiting. The drug is tolerated without reaction even in patients known to be sensitive to the related compound, Furacin. Clinical studies have demonstrated rapid clinical response of cases of cystitis prostatitis, and pyelonephritis, including infections due to organisms resistant to the usually employed antibiotics and sulfonamides. Medication should be continued for at least three days after a sterile urine is achieved.

"Among the lower beings even more than among the higher animals and plant species, life destroys life"

L. Pasteur and J Joubert (1877)

TABLE 1

SUMMARY OF DOSAGE AND ADMINISTRATION OF ANTIMICROBIAL AGENTS

Antibiotic	*Oral*	*Intramuscular*	*Intravenous*	*Intrathecal*
Penicillin	3 to 5 times intra muscular dose.	100 000–10 000 000 U daily depending on severity and type of in fection. Crystalline q 3 h. Repository 1 to 2 daily DBED 5 to 7 days.	600 000 units or continuous drip supplements I M. ad *ministration when high* blood levels and rapid effect are desired.	Rarely indicated.
Streptomycin	0 5 to 1 0 Gm. daily	1 to 2 Gm. daily for 5 to 7 days for gram nega tive infections. 1 Gm. twice a week with PAS or INH for tuberculosis.	Not recommended.	50 to 75 mg daily depending on se- verity and type of infection.
Chloramphenicol	1 to 4 Gm. daily in divided doses q 4 to 6 h.	Seldom used because of local tissue reaction.	700 mg in propylene glycol q 4 h. caution is advised.	Not recommended.
Chlortetracycline	1 to 2 Gm. daily in divided doses q 4 to 6 h.	Not recommended.	100 and 500 mg. in sterile water saline, or glucose.	Not recommended.

TABLE 1 (Continued)

Antibiotic	*Oral*	*Intramuscular*	*Intravenous*	*Intrathecal*
ytetracycline	1 to 2 Gm. daily in divided doses q 4 to 6 h.	200 to 300 mg daily in divided doses q 8 to 12 h	0 5 to 2.0 Gm. daily in di vided doses q 12 h in glu cose or saline	Not recommended
Tetracycline	1 to 2 Gm. daily in divided doses q 4 to 6 h.	200 to 300 mg daily in divided doses q 8 to 12 h.	0 5 to 2 0 Gm daily in di vided doses q 12 h. in glu cose or saline.	Not recommended
Erythromycin	1 5 to 4 0 Gm. daily in divided doses q 4 to 6 h	Not recommended	250 mg q 6 h	Not recommended
	200 mg maximum daily in divided doses q 6 to 8 h.	2.5 mg /kg and not to exceed 200 mg daily in divided doses q 6 to 8 h.	Not recommended	Not recommended
	Not to exceed 100 000 units daily in divided doses q 6 h.	50 000 to 100 000 units daily in divided doses q 6 h. In 1 ml. 1% procaine.	Not recommended	5 mg daily for 3 days or less, then 5 mg on alternate days. Not recommended except in selected cases.

2

Antimicrobial Combinations and Adjuvants

COMBINED ANTIMICROBIAL THERAPY

IN this antibiotic age one finds the bacterial world revolting against Man's attack on its population Fortunately for Man the microorganisms which are responsible for most acute infections (the pneumococcus, meningococcus gonococcus, many strains of streptococcus and the spirochete of syphilis) have as yet not developed any effective defense mechanism against the antibiotic agents On the other hand, there is an increasing number of microorganisms the staphylococcus in particular which possess or can develop the means of resisting these agents The discovery of a way to halt this trend of increasing antibiotic resistance in bacteria, as well as the successful management of the naturally resistant organisms to these agents represents a real challenge in this field. The introduction of newer antibiotics with wider ranges of antimicrobial activity and the ability to interfere with the adaptive processes of microorganisms so as to preclude the development of drug resistance offer the best hope of solving this problem However until this is realized, we should not overlook the possible utility of the now available antibiotics especially when they are administered in various combinations

In view of our lack of understanding of the fundamental mechanism of antibiotic activity it must be presumed that

these various antibiotics act through different mechanisms so that a combination of agents might well be expected to exert a more complete action against certain microorganisms than a single agent.

Not infrequently the practicing physician is confronted with the problem of having at his disposal a number of clinically useful agents each of which alone is incapable of producing the desired effect in a given case. The temptation to use a combination of antibiotics in such instances represents a practical everyday problem. What reliable information is available which will assist the practicing physician in selecting the antibiotics to be used in combination under appropriate indications?

In order to give an answer to this query there has been within recent years a considerable number of studies done dealing with antibiotic combinations Obviously the most desirable effect to be gained in polyantibiotic therapy is that of synergism, which effect is greater than that to be expected from a simple summation of the independent actions of the several antibiotics employed. Conversely one of the serious undesirable results of polyantibiotic therapy may be antagonism where the net result may be not only less than the simple additive effect to be expected if the several drugs were to act independently but it may be less than would result from the effect of either drug used alone Jawetz and his colleagues at the University of California Medical School have reported both *in vitro* and animal experiments which indicate an antagonism between penicillin and the wide spectrum antibiotics. These workers demonstrated *in vitro* that the bactericidal rate of penicillin was retarded by the addition of either chloramphenicol, chlortetracycline or oxytetracycline The observed interference was characterized as being unilateral, occurring maximally when the bac-

tericidal activity of penicillin was greatest and the concentration of the antagonizing agent was bacteriostatic, and yet, the combination was capable of a progressive bactericidal action which ultimately sterilized the culture. Subsequent *in vivo* experiments utilizing mice infected with Group A streptococci revealed a higher mortality rate in animals receiving both penicillin subcutaneously and chloramphenicol intraperitoneally than in those receiving penicillin alone. Other workers have been unable to confirm the above observations and in some instances even reported a synergistic effect with the same combinations reported by Jawetz as being antagonistic Furthermore clinical substantiation of antibiotic antagonism has not been forthcoming, except for a single report in which a higher mortality was observed in pneumococcic meningitis treated with oxytetracycline and penicillin than when penicillin was used alone In this instance one questions the rationale of employing polyantibiotic therapy in that the pneumococcus is known to be highly susceptible to penicillin alone Furthermore it has been shown that in such highly susceptible organisms synergistic activity can be rarely demonstrated Whereas antibiotic antagonism is conceded at present to have little if any clinical importance there is not only laboratory but also clinical evidence that polyantibiotic therapy may result in definite synergistic effect against certain bacteria (such as penicillin and streptomycin in enterococcal infections streptomycin and either chloramphenicol oxytetracycline, or chlortetracycline in brucellosis penicillin and bacitracin in staphylococcal infections and para aminosalicylic and dihydrostreptomycin in tuberculosis) Such combinations not only offer increased antibacterial effect, but also may delay the appearance of drug resistant organisms in certain instances

Recently Eisenberg and his associates at the Philadel phia General Hospital (Blockley Division) have reported on the synergistic action of polyantibiotic therapy on a variety of bacteria, both in the laboratory and in clinical practice. *In vitro* studies employing the various antibiotics (penicillin, streptomycin, chloramphenicol, oxytetracycline and chlortetracycline) singly and in twenty-six different combinations against strains of *Staphylococcus aureus* and *Klebsiella pneumoniae* type A indicated that combinations of chloramphenicol, oxytetracycline and penicillin and chloramphenicol, oxytetracycline and chlortetracycline showed both bacteriostatic and bactericidal synergism against these organisms respectively Further evaluation of these two combinations against individual composite cul tures of *Staphylococcus aureus Streptococci (viridans pyogenes enterococcus) Coliforms S typhosa Klebsiella pneumoniae* types A and B *Ps aeruginosa*, and *Proteus sp.*, total ling 258 individual strains indicated that the combination of chloramphenicol, oxytetracycline and chlortetracycline (COC) was superior to the chloramphenicol, oxytetracy cline penicillin combination, as well as to the same agents used singly

As additional corroboration for the above findings these same workers surveyed the antibiotic susceptibility of 2173 individual bacteria, in order to compare the incidence of susceptibility to the chloramphenicol-oxytetracycline-chlor tetracycline combination with that of its individual con stituents Of the 1093 gram positive bacteria studied, it was found that ninety five per cent were susceptible to COC, as compared to eighty-eight, eighty-six, and eighty three per cent for chloramphenicol, chlortetracycline and oxytetra cycline respectively Considering the 843 strains showing a high incidence of penicillin resistance, ninety four per cent

were found to be sensitive to COC eighty five per cent to chloramphenicol and eighty per cent to either chlortetracycline or oxytetracycline. Of the 1080 gram negative bacteria studied, seventy per cent were susceptible to COC, sixty-one per cent to chloramphenicol, forty six per cent to streptomycin, thirty-eight per cent to oxytetracycline and twenty seven per cent to chlortetracycline. Of the 2173 bacteria studied, eighty three per cent were susceptible to COC as compared to seventy five, sixty-one and fifty-six per cent to chloramphenicol, oxytetracycline, and chlortetracycline respectively Although the quantity of chloramphenicol, oxytetracycline and chlortetracycline was only one third that when these antibiotics were used alone the incidence of susceptibility to COC was found to be significantly greater than that to the individual antibiotics

Preliminary clinical studies at the Philadelphia General Hospital (Blockley Division) indicate that a combination of chloramphenicol oxytetracycline and chlortetracycline is just as effective therapeutically as penicillin in the treatment of pneumococcal pneumonia and superior to its use alone in Klebsiella pneumonia. In addition it has been shown that the combination COC has merit and is worthy of extensive trial in the treatment of refractory urinary tract infections especially in patients with diabetes mellitus as well as in such conditions as typhoid fever and infections due to the Bacteroides group

Certainly the status of polyantibiotic therapy in present day clinical medicine is still largely undetermined particularly in view of our lack of understanding of the mode of action of these drugs when used in combination. Until these fundamental problems are more fully understood, or until such time as sufficient evidence has been accumulated to indicate which combinations may or may not be useful,

the practicing physician can best contribute to the welfare of his patient and to the advancement of knowledge in this field by following certain principles of antimicrobial therapy Although most infectious diseases are successfully treated with the laboratory establishment of a definite etiologic diagnosis the fact remains that one can employ antibiotic therapy more intelligently if the infecting agent, or agents are known. Certainly those cases failing to respond to therapy deserve the benefit of necessary laboratory studies One should use doses of single antibiotics that have proved adequate and effective as in most infections caused by a single organism and in certain types of mixed infections a single agent can be used effectively For those infections where the offending organism proves resistant to single drugs by laboratory tests or by adequate therapeutic trial, then should polyantibiotic therapy be considered. Where there is already adequate clinical proof that the use of multiple agents may be expected to yield beneficial effects the proper combination should be employed immediately In those cases where clinical evidence of effective combined therapy is lacking, it is necessary to resort to additional laboratory procedures in hopes of finding a combination of drugs which will prove more effective than a single agent alone Unfortunately the laboratory has not as yet been able to provide an empirical formula for this purpose. However it can furnish valuable information which may serve as a guide in the selection of various combinations Certainly we are justified in employing antibiotic combinations clinically in those instances where appropriate tests fail to demonstrate definite antagonism

"If many drugs are used for a disease all are insufficient"
Sir William Osler (1849-1919)

CORTISONE AND ANTIBIOTICS IN INFECTIONS

Cortisone is well known to have a deleterious effect on humoral resistance to a wide variety of infections clinical and experimental. Infections with tubercle bacilli streptococci staphylococci and poliomyelitis virus are among those in which the enhancing effect of cortisone has been demonstrated. Considerable attention has been given the possibility that this is due to the action of cortisone on antibody formation The effect of cortisone on infections however appears to be too rapid to be explained solely on the basis of depression of antibody formation, and Thomas has presented evidence which suggests that the effect of cortisone is to blockade the reticuloendothelial system impairing its normal capacity to remove fix or detoxify bacteria

Occasionally there may be justification for treating overwhelming infections with corticotropin or cortisone in conjunction with intensive antibiotic therapy Certainly the acute circulatory collapse accompanying the Waterhouse-Friderichsen syndrome represents a definite indication for replacement therapy with this hormone Smadel and his associates have demonstrated the effectiveness of cortisone when given in conjunction with chloramphenicol in the treatment of typhoid fever Similarly Workman and his co-workers have observed that cortisone, combined with chloramphenicol, shortened the clinical course and signs of intoxication in Rocky Mountain spotted fever Likewise preliminary reports indicate the value of combined antibiotic-cortisone therapy in selected cases of acute brucellosis infectious mononucleosis and infectious asthma. In addition hydrocortisone topically in combination with various antibiotics has been used successfully in stubborn dermatological and ophthalmological infections The hazards of steroid

3

Laboratory Aspects of Antimicrobial Therapy

Ever since the introduction of the sulfonamides in the 1930's the importance of the microbiology laboratory to the clinician has steadily increased. In addition to its original function of isolating and identifying pathogens the microbiology laboratory is now a significant factor in contributing to the delineation of specific antimicrobial therapy which would, in many instances be virtually impossible of accomplishment except on purely empirical grounds. Primarily as a result of antibiotic sensitivity surveys it has been established that different genera of microorganisms are variable with respect to their response to the activity of antibiotics By the same means it has been shown that this variation extends beyond generic limits to individual strains within a specified genus. *In vitro* microbiological studies in addition to demonstrating that sensitive organisms can develop resistance to antimicrobial agents under appropriate conditions also serve as the signal which indicates trends of changes of sensitivities and development of cross resistance to antibiotics. In many instances the reasons for success or failure of specific agents in clinical usage have been explicable on the basis of results of *in vitro* testing. This is not meant to convey the impression that such testing is infallible but it is generally agreed that by and large the anticipated clinical results as predicted

by *in vitro* tests correlate well with those actually occurring in the clinic.

Additionally the microbiology laboratory can be of help to the clinician in the evaluation of activity of antibiotic combinations in the assay of body fluids and in alerting the clinician as to the probable development of a super infection as a coincident complication of antimicrobial scribed dosages

Antibiotic Susceptibility Tests

One of the several important criteria upon which is based the selection of an agent to be used in the treatment of an infection is the *in vitro* relative susceptibility of the etiologic agent to the various antibiotics It should be emphasized that the clinician can in many instances prescribe specific therapy without recourse to susceptibility testing. The many recorded instances of dramatic clinical response following the use of antibiotics selected without benefit of prior *in vitro* sensitivity tests are ample evidence for the reliability of the clinician s antibiotic experience. Nevertheless, there is equally little doubt that on many occasions he is confronted with the problem of treating an infection in which either the etiologic agent has not shown uniformity of susceptibility to the same single antibiotic agent or in which the etiologic agent and site of infection is obscure In these instances, susceptibility tests can be helpful

Without debating the pros and cons of the practical importance of the results of such determinations, it would appear that there would be small, if any argument on two relative points. First, that at the present time a substantial number of clinicians request these determinations because they feel that the information obtained thereby is of definite value in defining specific therapy Second, that as a con

sequence of these requests most hospital laboratories, even those with modest bacteriological facilities are required to perform these tests with varying frequency The evidence that (a) microorganisms vary as to antibiotic susceptibility and may develop resistance to them under appropriate con ditions (b) observed clinical response is for the most part in good agreement with results indicated by *in vitro* tests and (c) continuing research efforts by pharmaceutical com panies and others to find new antibiotics all point to the probability that requests for these tests will not diminish, but may be expected to increase

As has been previously pointed out by one of us (G M E.) there are two basic types of susceptibility tests the serial dilution and agar plate diffusion. The relative merits and disadvantages of these procedures have been discussed in considerable detail by others elsewhere Suffice it to say that while the serial dilution test in liquid media is reliable and accurate in direct proportion to the effort which is made to insure constancy of conditions and until recently was the sole *in vitro* procedure by means of which the effects of two or more antibiotics could be determined, it is too time consuming, laborious and expensive to be considered prac tical as a routine hospital procedure Equally important is the fact that the comparatively precise data afforded by the test is disproportionate to its clinical usefulness with the result that most laboratories performing susceptibility tests resort to some modification of the filter paper agar diffusion procedure. Agar diffusion methods utilizing antibiotic reser voirs in the forms of filter paper disks or cups of one sort or another or employing the principle of ditching or welling, while no substitute for serial dilution tests lend themselves more conveniently to routine use and are clinically reliable provided the results are not given excessive quantitative

interpretation and are used solely as a qualitative guide in defining susceptibility Unlike the serial dilution tests the available agar disk procedures neither permit evaluation of antibiotic combinations nor lend themselves readily to a determination of whether the inhibition which is observed is bacteriostatic or bactericidal.

In order intelligently to interpret the results obtained with antibiotic susceptibility test procedures, it is necessary to consider several points First, what is meant by the term antibiotic susceptibility? Second, an appreciation of the scope of the interpretation which should be placed upon *in vitro* sensitivity tests Third, an understanding of the principles which underly these tests

An antibiotic susceptibility determination in the labora tory either by a serial dilution test or an agar diffusion test, is actually the measuring of an antibiotic concentration, or range of concentrations which is effective in producing some degree of growth inhibition of the test organism This result is a numerical expression of little or no significance unless it is interpreted with regard to some reference stand ard. If the reference standard is the inhibiting concentra tion for a second organism then it is possible to describe the susceptibility of the first in terms of the second. Thus, while the results of the tests for any one organism have a more or less absolute value, the interpretation of them in terms of susceptibility should only be a relative one. Consequently antibiotic susceptibility is an expression of relative and not absolute value If we are to speak of susceptibility what is to be the reference standard? In our opinion the clinical distinction between "resistant" and "susceptible should be made with reference to the antibiotic concentra tion obtainable in blood of patients receiving some dosage of antibiotic. For example a dosage schedule which pro-

duces blood concentrations below those which are necessary for inhibition as indicated by *in vitro* tests automatically labels the infecting organism as "resistant." However if as a result of increased dosage or some other means the blood levels are elevated beyond the *in vitro* inhibiting concentration, the same organism is now designated as "susceptible" For clinical purposes then it is not necessary to know the finite concentration required for inhibition as long as it is less than the concentration attainable in blood with prescribed dosages

We are fully cognizant that the critical and effective concentration of an antibiotic is probably that which exists in the tissues at the actual site of infection rather than that which is present in the peripheral circulation However in view of the obvious difficulties in determining tissue concentrations and the rather universal agreement that blood concentrations correlate well with clinical response the establishment of blood level concentrations as a criterion is understandable From the clinical standpoint, then, it is dosage and concomitant blood level concentration which govern the practical distinction between resistance and susceptibility Hence all that should be required of a susceptibility test is an observation of *in vitro* inhibition regardless of degree, by an antibiotic concentration equivalent to the average maximum level obtainable with specified dosages. It immediately becomes obvious that the clinical interpretation of resistance or susceptibility is predicated upon a clear definition of (a) blood concentration of antibiotic and (b) the dosage that is used to obtain these blood concentrations

In our laboratories we have for some time been utilizing as a criterion for differentiation of resistance and susceptibility the concentration of antibiotic which can be expected in average patient s blood when the most

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commonly prescribed dosage of the antibiotic is administered. The criteria which we have set up are shown in the accompanying Table 2 and are based upon the utilization of a filter paper disk procedure which has been previously described. It is to be observed that we pay little attention to the size of the zone of inhibition and that the only matter of importance as far as we are concerned is whether or not evidence of inhibition as manifested by the presence of a zone of any size is apparent. For instance utilizing a disk which contains one unit of penicillin, if a zone of inhibition is obtained the organism present is reported as susceptible, whereas if no zone of inhibition is obtained, the organism is reported as being resistant. At this point, great emphasis should be put on the fact that in our opinion, a report such as has just been described does not necessarily contraindicate the clinical use of penicillin in the illustration under consideration It merely means that under the conditions of the *in vitro* procedure the test organism is not susceptible to a concentration of one unit, or less of penicillin, a concentration which one can ordinarily expect to find in the blood of average patients when these patients receive penicillin as procaine 300 000 units daily or as crystalline 100 000 units every three hours This same organism, on the basis of a higher dosage, or on the basis of retarded penicillin excretion, could very well be susceptible, in view of the fact that higher blood concentrations can be expected under the latter conditions. It is our feeling that a susceptibility report from the laboratory should not constitute the sole basis upon which the selection of an antibiotic for clinical use is to be based. Rather do we feel that the report should be considered as just one more factor among several which assist in determining whether or not a given antibiotic should be used. The pharmacologic properties of the drug

itself that is a knowledge of the specific tissues in which it penetrates (Table 3) the location of the infection the presence or absence of impaired renal function the state of vascularity in the patient are also factors which will determine the clinical success of a given antibiotic and it is the sum total of the consideration of all these factors which should determine the selection of an antibiotic and which will prognosticate the outcome of its use The relative susceptibility to several antibiotics of representative organisms encountered at the Philadelphia General Hospital (Blockley Division) are shown in Table 4

A few words are in order regarding the practice of designating antibiotics as being either bacteriostatic bactericidal or both It is our experience that in many instances the selection of an antibiotic is determined by the reputation which it has acquired as being either a static or lethal agent. In practice it is often extremely difficult to distinguish between bacteriostatic and bactericidal effects Strictly speaking, the term bacteriostasis should apply only to those situations in which there is no change in the number of viable bacteria during the time of exposure to an inhibitory compound That it is frequently impossible to satisfy this criterion is readily appreciated when it is realized that when the reproductive process of an organism is retarded the organism may readily die of starvation or senescence and after an appropriate lapse of time there may be a gradual but significant decrease in total numbers It has been stated that no chemical substance is known which in the presence of a culture media and under conditions suitable for their growth holds the number of bacteria constant and therefore no substance can strictly be said to have a bacteriostatic action. Bactericidal activity is usually interpreted as referring to a situation where there is a rapid destruction of organisms

resulting in a diminution of their number Therefore, as is well known, all antibiotics can be either bacteriostatic or bactericidal, depending on the concentration. It would seem that the sole valid distinction between bacteriostatic and bactericidal effects rests on the rate at which bacterial numbers decline the rate being greater with bactericidal than with bacteriostatic agents From the clinician's point of view however the terms bacteriostatic and bactericidal are utilized in defining the activity of antibiotics under those conditions of concentration which can be obtained in the body In the case of some antibiotics even under conditions of maximal dosage the blood and tissue levels attainable are such that at best they can manifest only a static activity On the other hand, there are agents like penicillin and streptomycin, which under conditions of ordinary dosage are present in concentrations which can produce a lethal effect and consequently are referred to as bactericidal agents The question of the necessity of maintaining concentrations of antibiotics in blood and tissues which are lethal in order to obtain satisfactory therapeutic response is a debatable one, in view of the fact that some of our so-called bacteriostatic agents have also shown themselves capable of producing dramatic responses It therefore seems largely a question of the type of infection and the nature of the etiologic agent which is involved as to whether or not a bacteriostatic or bactericidal effect is desired It is generally agreed that in some diseases, especially subacute bacterial endocarditis it is necessary to maintain a bactericidal concentration in order to eradicate completely all the organisms involved in the infection If this is not done experience has shown that the infection will recur so that this is an instance where the maintenance of a lethal effect is desired and can be obtained only through

the use of an antibiotic or combination of agents which is found to produce blood concentrations which are lethal

For the majority of antibiotic therapeutic problems which confront the clinician on a day to day basis it is not necessary for him to know either the bacteriostatic susceptibility or bactericidal susceptibility of many organisms causing disease As a matter of fact, there are certain classes of organisms which have been consistently shown to be susceptible to all the known indicated antibiotics These include *Streptococcus viridans* and *pyogenes* *Pneumococcus* *Gonococcus* *Meningococcus* and *Hemophilus* organisms On the other hand there are certain groups of organisms which have been shown to be naturally resistant to most or nearly all of the available antibiotics. In this respect we refer specifically to *Proteus* and *Pseudomonas* with the exception that the latter group of organisms are quite susceptible to polymyxin B Between these two extremes lie the genera including *Staphylococci* *Salmonella* *Enterococci* *Escherichia* *Shigella* *Klebsiella* and *Paracolon* It is with diseases in which these organisms are involved that the clinician usually requires the assistance of *in vitro* susceptibility tests in selecting specific therapy and it is in these instances that he may from time to time require information as to the bacteriostatic and bactericidal concentrations of an antibiotic Thus the laboratory must be prepared to furnish both types of information a condition which cannot be fulfilled by the performance of either the routine serial dilution or the agar diffusion tests The determination of bactericidal concentration requires a more elaborate procedure and can be performed most conveniently in conjunction with the serial dilution test. These procedures comprise the preparation of subcultures from those tubes of a serial dilution series which show no microscopic growth. In most instances this

is accomplished by taking a loopful, or some other small aliquot of the test portion, transferring it to a fresh container of culture medium devoid of antibiotic and observing whether or not growth occurs in the subculture While this sounds like a relatively simple procedure, a number of dangers are associated with it (a) A loopful of test mixture may on the basis of chance alone contain no viable organisms particularly if the original number of organisms used as an inoculum is small. (b) A bacterial population consists of individuals of varying antibiotic susceptibility While a given antibiotic concentration may be sufficient to inhibit the majority of individuals in such a population, a small number of resistant forms remain undetected and will require a longer incubation time to make their presence apparent as macroscopic growth. Thus a loopful of material from such a population may also on the basis of chance alone contain no viable organisms (c) Sufficient antibiotic may be carried over to the subculture so as to furnish an inhibitory concentration for the period of time during which such subcultures are grown This is more likely to occur when attempts are made to increase the amount of material for subculture In the case of antibacterial agents for which specific inactivators are known, *e g* penicillin and sulfonamides this difficulty is easily circumvented by the use of specific inactivators However in the case of some of the newer antibiotics specific inactivators are not available and other devices such as dilution must be used. We have recommended that in the determination of bactericidal activity the entire contents of the tubes which in the serial dilution tests show no growth should be evaluated for the presence of organisms and that the finding of a single viable colony indicates less than complete bactericidal effect. In summary therefore it is our feeling that laboratory studies of suscepti

bility should include a determination of minimum inhibiting concentration a determination of whether the inhibition is temporary or permanent, and a determination of the approximate number of surviving bacteria All these determinations should be made in appropriate sequence on the same bacterial population These however do not represent the necessities of routine testing but rather the necessities of testing for specialized situations

Over a period of several years there have been numerous reports emphasizing the increased frequency with which organisms develop resistance to one or more of the antibiotics Concurrently with this trend we have seen the introduction of a number of new antibiotics each of which at the time it was first introduced was found to be effective against those organisms which had developed resistance to the antibiotic which had been previously used. But, as time went on, and the frequency increased with which the newer antibiotics were used for treatment it was also observed that the incidence of resistance to these newer antibiotics likewise increased Thus the problem of developing resistance of organisms became an alarming one and it was only natural that considerable thought would be directed toward the possibility of using antibiotics in combination in an effort to forestall the development of resistance of organisms to all of our antibiotics. Other possible areas of utility visualized for antibiotic combinations are treatment of mixed infections cases in which diagnosis or identity of causative organisms is not immediately apparent, expansion of the effective antimicrobial spectrum of the known drugs beyond the limits accomplished by the individual antibiotic, reduction of the incidence of superinfections and reduction of frequency and severity of untoward reactions provided

diminution of dosage would be effective without material sacrifice of therapeutic activity

As studies of the effect of one or more antibiotics upon the activity of another increased, it became apparent that while one investigator was ascribing synergistic activity to a certain antibiotic combination, another investigator using the same combination was observing antagonistic activity That the ultimate outcome of such conflicting reports should have resulted in confusion is therefore not surprising, especially since the definition of synergism and antagonism usually reflected the individual background of the investigator were he microbiologist, pharmacologist, or clinician and to each of whom the terms had a different meaning. The observation that chlortetracycline and chloramphenicol, frequently reported as antagonizing the rate of bactericidal activity of penicillin, could not be substantiated by other workers who pointed out that the effect observed varied with the concentration of agents and the species of the test organism is a case in point. The combination of chlortetracycline with chloramphenicol, or streptomycin has been reported as showing additive or synergistic effect. Oxytetracycline has been reported as having the same effect as chlortetracycline on penicillin. Combinations of oxytetracycline with chlortetracycline chloramphenicol, or streptomycin have been reported as synergistic. Polymyxin B has been reported as synergistic with other antibiotics *in vitro* but antagonistic towards penicillin and streptomycin *in vivo* As the literature on the activity of antibiotic combinations is reviewed, one cannot help but be struck by the following facts First, that the major effort in the study of antibiotic combinations has been confined to observations *in vitro* on a limited number of bacteria. A fewer number of studies are concerned with attempts to apply these findings to experimental ani-

mals The rather scant reports of antibiotics in Man are largely limited to the use of such combinations as penicillin streptomycin in enterococcal endocarditis streptomycin PAS INH in tuberculosis penicillin-chlortetracycline in pneumococcal meningitis and bacitracin penicillin in staphylococcal infections which are amenable to local treatment. At the present time it is generally conceded that the phenomenon of antibiotic synergism or antagonism is dependent upon the specific bacterial species employed and the relative proportion of the agents to which they are exposed From a clinical standpont, however antibiotic antagonism appears to have little significance provided that the individual agents used in combination are utilized in full therapeutic dosages.

Cross Resistance to Antibiotics

The question of cross resistance among antibiotics has fundamental implications The mechanism whereby antibiotics exert their activity is not established and it is not unlikely that the mechanism of acquisition of resistance may be intimately related to these modes of action In general it can be stated that the development of cross resistance amongst antibiotics has been limited largely to chemically related antibiotics The relationships can be summarized briefly as follows Among the tetracycline drugs the development of mutual cross resistance occurs rather frequently (Table 5) The relationship between cross resistance to the tetracycline drugs and chloramphenicol, on the other hand, appears to vary with the bacterial species some developing significant resistance while others show little or none The development of resistance to the tetracyclines does not appear to be accompanied by the concomitant development of resistance to penicillin or streptomycin Development of

resistance to streptomycin is not necessarily accompanied by resistance to neomycin. An interesting suggestion arising from cross resistance studies indicates that the development of resistance by an organism to one antibiotic may actually lead to increased susceptibility to other antibiotics. This has been demonstrated in the case of streptomycin where organisms developing resistance to this antibiotic become more susceptible to the tetracyclines.

Antimicrobic Spectrum of Antibiotics

By the antimicrobic spectrum of an antibiotic, we refer to the diversity of different genera of microorganisms against which the specific antibiotic is effective. Table 6 shows the antimicrobic spectra of the currently available, clinically useful antibiotics. It is pointed out that this chart is a practical one and is to be used only as a ready reference with the realization that individual strains of microroganisms within each of the genera shown may be variable in respect to their reaction. From this chart, it should be apparent that penicillin and bacitracin have very similar antimicrobic spectra, although the latter agent is usually more effective against *Streptococcus fecalis*. Chloramphenicol is the drug of choice against the typhoid bacillus. Its second widest application probably resides in the treatment of penicillin-resistant staphylococcal infections. Oxytetracycline has been shown to be effective in intestinal amebiasis. Erythromycin has been shown to be of great value in the treatment of staphylococcal and streptococcal infections resistant to other antibiotics. Polymyxin B has a peculiar predilection for Pseudomonas organisms.

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TABLE 2

CRITERIA FOR INTERPRETATION OF SUSCEPTIBILITY
(Philadelphia General Hospital—Blockley Division)

Antibiotic	Dosage Schedule	A Max Blood Level Resulting From Indicated Dosage Units or mcg /ml	Relative Susceptibility When Inhibition Zone Is	
			Present	Absent
Penicillin	300 000 units Procaine daily or 100 000 units crystalline q 3 h.	1 0	1 unit or less S	more than 1 unit R
Streptomycin	0.5 Gm. b.i.d.	15	15 mcg or less S	more than 15 mcg R
Chloramphenicol	0.5 Gm. q 6 h.	15	15 mcg or less S	more than 15 mcg
Chlortetracycline	0.5 Gm. q 6 h.	4	4 mcg or less S	more than 4 mcg R
Oxytetracycline	0.5 Gm. q 6 h.	6	6 mcg or less	more than 4 mcg
Tetracycline	0.5 Gm. q 6 h.	5	5 mcg or less	more than 5 mcg
Erythromycin	0.3 Gm. q 6 h.	3	3 mcg or less S	more than 3 mcg R

Note: S = Susceptible
R = Resistant

TABLE 3

TISSUE AND BODY FLUID DISTRIBUTION CHARACTERISTICS OF ANTIBIOTICS WHEN GIVEN BY THE USUAL ROUTE OF ADMINISTRATION

Antibiotic	*Spinal Fluid*	*Urine*	*Bile*	*Gastro-intestinal*	*Pleural Cavity*	*Peritoneal Cavity*
Penicillin	Poor with ordinary dosage unless meninges are inflamed good with high doses. Neo-Penil appears to have unique ability to traverse hemato-cephalic barrier	Good	Moderate diffusion	Fair if oral penicillin is used largely inactivated.	Good, depending on dosage.	Fair readily into ascitic fluid.
Streptomycin	Poor except in cases of inflamed meninges.	Good	Good	Largely unabsorbed.	Moderate	Moderate
Chlortetracycline	About 1/2 of blood concentration.	Good	About 1/4 blood conc.	Rapid	Poor	Poor
Oxytetracycline	Poor	Good	Good	Rapid	Good	Good
Tetracycline	About 1/4 of blood concentration.	Good	Good	Rapid	Good	Good

TABLE 3 *(Continued)*

Antibiotic	*Spinal Fluid*	*Urine*	*Bile*	*Gastro-intestinal*	*Pleural Cavity*	*Peritoneal Cavity*
Chloramphenicol	Lower and slower than blood.	About 10% in active form.	Good as in blood	Rapid		
Erythromycin	Poor	Good	Good	Rapid. No effect on gram-negative flora.	Poor ¼ of blood conc.	About ½ of serum level.
Nitrofurantoin	None	High	None	High	None	None
Sulfonamides	Generally good to all tissues, but degree depends upon specific type in use.					

TABLE 4

RELATIVE ANTIBIOTIC SUSCEPTIBILITY OF BACTERIA ISOLATED FROM ROUTINE CLINICAL SPECIMENS†

Organism	*Total Strains*	*Per Cent Susceptible to.*				
		P	*S*	*C*+	*O*	*C*++
Str viridans	107	99 1	——	100	100	100.
Str pyogenes	38	100	——	100	100	100
D pneumoniae	105	100	——	100	100	100
M p var aureus	475	29 9	——	85 0	81 8	87.5
Alpha enterococcus	283	33.2	——	82.8	78 4	82.8
Beta enterococcus	85	28.2	——	57 7	55.3	79 8
Total	1093	46.5	——	86.0	82.8	88.5
H influenzae	47	——	93 6	100	100	100
Coli-aerogenes	447	——	61 0	33 4	48 7	83.3
Klebsiella Sp	139	——	43.2	40.2	51 7	65 4
Paracolon Sp	109	——	49 6	20.2	29 4	64 1
Proteus Sp	224	——	23.2	3 1	7 9	32.1
P aeruginosa	114	——	9 7	4 4	18 4	6.1
Total	1080	——	45 7	26.5	37 7	60.8
Grand Total	2173	——	——	56 4	60 6	74.8

Note †Urine, sputum, blood, C.S.F., exudates
P = penicillin
S = streptomycin
C+ = chlortetracycline
O = oxytetracycline
C++ = chloramphenicol

TABLE 5

Comparative *In Vitro* Susceptibility to the Tetracyclines of Bacteria Isolated from Clinical Specimens

Organism	Number of Strains	*Per Cent Susceptible to*		
		C	O	T
Micrococcus pyogenes var. albus	46	56.4	63.1	60.8
Micrococcus pyogenes var. aureus	110	63.2	61.2	60.2
Alpha streptococcus	102	45.0	42.2	42.2
Escherichia Sp	60	40.0	55.0	53.3
Klebsiella Sp	177	33.9	41.2	39.0
Paracolobactrum Sp	46	28.3	39.1	45.6
Proteus Sp	49	4.0	4.0	4.0
Pseudomonas Sp	45	0.0	28.9	0.0

Note. Two strains *D. pneumoniae*, two strains *Str. viridans*, three strains *N. intracellularis* and seven strains *H. influenzae* uniformly susceptible to all tetracyclines. Evaluation made by filter paper disk procedure. Chlortetracycline (C) = 4 mcg., oxytetracycline (O) = 6 mcg., and tetracycline (T) = 5 mcg. While majority of strains tested (eighty-eight per cent) showed similarity of susceptibility pattern, either sensitive or resistant simultaneously to the three tetracyclines, twelve per cent showed some variation in that while resistant to one or two of the three tetracyclines they were nevertheless susceptible to the other member or members of the group. This would indicate that while cross resistance to tetracyclines occurs in many organisms, it does not occur universally.

TABLE 6
In Vitro Spectra of Useful Antimicrobial Agents

Agent	BACTERIA			*Rickettsiae*	*Virus*
	Gram-Positive	*Gram-Negative*	*Spirochete*		
Penicillin	Actinomyces Bacillus Clostridium Corynebacterium Micrococcus Streptococcus Diplococcus	Neisseria Fusobacterium	Leptospira Borrelia Treponema		
Streptomycin	Mycobacterium Corynebacterium	Brucella Escherichia Klebsiella Hemophilus Pasteurella Donovania Some Proteus			
Tetracyclines	Bacillus Micrococcus Streptococcus Diplococcus Clostridium	Brucella Vibrio Escherichia Neisseria Hemophilus Klebsiella Donovania Pasteurella Some Salmonella and Shigella	Leptospira Borrelia Treponema	Q Fever Rocky Mt. Spotted Fever Scrub Typhus Typhus Rickettsial pox	Lymphogranuloma venereum Mumps (orchitis) Psittacosis

TABLE 6 (Continued)

Agent	BACTERIA			*Rickettsiae*	*Virus*
	Gram-Positive	*Gram-Negative*	*Spirochete*		
Chloramphenicol	Bacillus Micrococcus Streptococcus Corynebacterium Actinomyces Clostridium	Brucella Escherichia Neisseria Hemophilus Klebsiella Pasteurella Salmonella, incl S. Typhosa Some Shigella Some Proteus Vibrio		Q Fever Rocky Mt. Spotted Fever Scrub Typhus Typhus Rickettsial pox	Lymphogranuloma venereum Psittacosis
Erythromycin	Clostridium Corynebacterium Diplococcus Micrococcus Streptococcus	Hemophilus Brucella	Some Spirochetes		Psittacosis
Polymyxin		Pseudomonas Klebsiella Hemophilus Pasteurella Some Proteus Some Salmonella and Shigella			

TABLE 6 (*Continued*)

Agent	BACTERIA			*Rickettsiae*	*Virus*
	Gram-Positive	*Gram-Negative*	*Spirochete*		
	Actinomyces Clostridium Diplococcus Micrococcus Streptococcus	Neisseria Hemophilus Some Shigella	Treponema		
trofurantoin	Micrococcus Streptococcus Diplococcus Corynebacterium	Escherichia Proteus Kleisiella Neisseria Some Salmonella and Shigella Pasteurella	Borrelia		
	Streptococcus Diplococcus Nocardia	Neisseria (except Gonorrheae) Brucella Kleisiella Pasteurella Escherichia Hemophilus (ducreyi) Shigella Vibrio			Lymphogranuloma venereum

acteria = Approved Generic Nomenclature
se and Virus = Name of Disease

4

Complications of Antimicrobial Therapy and Their Management

There is no longer any doubt that the widespread use of antibiotic agents while resulting in the resolution of many problems in the field of infectious diseases has also served to create a number of new and sometimes perplexing ones Among these may be included the various untoward side effects which are seen more and more as the use and mis use of antibiotics become commoner Certain of these side effects are toxic, some are allergic and others seem to be related to the biologic activities inherent in the antibiotic agents themselves.

Most of the literature dealing with antibiotics is con cerned with the delineation of the triumphs produced by these drugs However the dangers and harmful sequellae of their uses have only recently begun to be stressed and appreciated. This is not to imply that the harmful effects that attend the use of antibiotics should discourage the physician from using them when they are indicated. However there appears to be developing a philosophy which tends to dis courage the indiscriminate use of antibiotics in cases or in situations where the indication for their use is entirely absent, or at most only slightly suggested.

Complications of antibiotic therapy can be placed in a number of broad categories

DERMATOLOGIC COMPLICATIONS

Dermatologic complications are mostly the result of sensitization, that is they are mainly allergic complications They occur in the form of various skin lesions appearing either during the course of therapy or soon after the administration of the same agent when it is administered in a subsequent course. Lesions which are seen may be transient and usually they increase in severity or lead to more serious consequences if administration of the antibiotic is continued. It has been estimated that at the present time one may expect *dermatologic complications in about four or five per* cent of all patients receiving antibiotic therapy

Dermatologic lesions occurring as a complication of antibiotic therapy are of several types First, a skin eruption is frequently seen in hypersensitivity to antibiotics as a macular or maculopapular drug eruption. It may be scarlatiniform or it may take on the characteristics of erythema multiforme. Occasionally it may become vesicular or purpural, if the reaction is severe enough or if the drug is not discontinued soon enough. The second type of skin eruption is urticaria or angioedema, which may be seen alone or as part of a serum-sickness type of hypersensitivity reaction to antibiotics A third type of dermatologic reaction is eczematous dermatitis This may eventually become widespread enough to produce a generalized exfoliation with severe weeping and oozing It may be particularly pronounced in the groins and around the feet, where the patient may have had a previous dermatophytosis Fourth, in individuals who work with antibiotics, or use them habitually locally there may be seen a true contact dermatitis.

This is particularly true in the case of penicillin and streptomycin and emphasizes the fact that application of anti biotics in ointment form to the skin is a good way to induce sensitization to these drugs Fifth mucous membrane mani festations are also seen as a complication of antibiotic ther apy This is most noticeable with all of the antibiotics but most frequently with the so-called wide spectrum anti biotics In these cases the usual manifestations appear as a red, inflamed oral mucosa with a swollen denuded tongue Occasionally there may be dermatitis at the angles of the mouth Sometimes the tongue is black and hairy and there may be an overgrowth of monilial organisms While *Candida albicans* is frequently grown in the labora tory from such lesions the exact relationship of this microorganism to the symptoms is still debatable In general, antibiotics *per se* do not stimulate the growth of yeasts but it seems that in some individuals *Candida albicans* grows excessively when the antibiotics destroy the associated bacteria. Stomatitis and glossitis may also occur as a true man ifestation of contact sensitivity of the mucous membranes particularly from the use of antibiotics contained in troches and lozenges It is estimated that this type of contact sensitivity is not infrequent and may occur in as high a percentage as fifteen to twenty per cent of patients who use these forms of local medication A large segment of medical practitioners feel that this form of treatment is not to be recommended at all. Other dermatological reactions that may occur following the parenteral administration of antibiotics are (a) fixed drug eruptions and (b) local in flammatory reactions at the injection site Local reactions at the sites of injection of antibiotics increase in intensity with successive injections and take on the characteristics of an Arthus-like phenomenon

The first and most important step to take in the management of dermatologic complications associated with antibiotic therapy *is to stop the administration of the drug.* For the urticarial, or serum sickness type of reaction, the antihistaminics in relatively large doses are very helpful. Pyribenzamine or benadryl in particular in doses up to 400 or 600 mg daily will often reduce the hives and relieve the pruritus even though they do not help the arthralgias or reduce the lymphadenopathy In dermatologic reactions attended by maculopapular eruptions eczematoid responses and mucous membrane manifestations, the antihistaminics are of little value In contact dermatitis, the antihistaminics again are without much use. For the more severe dermatologic manifestations such as urticaria, vesicular or bullous exfoliative eczematous or the contact type of hypersensitivity the use of corticosteroids is indicated These agents relieve the pruritus and weeping and quickly make the patient feel a lot better It would appear that this is an ideal situation for the use of ACTH or cortisone, since the condition to be treated is self limited in duration, provided of course that the administration of the antibiotic is stopped. The doses of corticosteroids required for relief may be large, but there is little danger since the therapy need not be continued for long As an example, hydrocortisone, 100-200 mg. daily for three days then diminished by decimals of 25 mg. each day will usually give good results Where the eruption is merely morbilliform and local, a bland emollient such as calamine lotion will be sufficient. Ointments and antihistamine-containing lotions or ointments are not employed, since these in themselves are also known to be sensitizers. For stomatitis complicating antibiotic therapy warm, saline mouth washes are recommended. Very frequently large doses of vitamin B complex are also given,

not because the vitamin B will give any outstanding therapeutic results but because the appearance of the oral mucosa reminds us of that which is usually seen in vitamin B deficiencies In vaginitis or perianal dermatitis douches or wet compresses of silver nitrate, 1 5000 are very helpful, particularly if there is a complicating moniliasis

GASTROINTESTINAL COMPLICATIONS

Adverse reactions in which the gastrointestinal tract has been involved have been reported during the course of treatment with all of the antibiotics The incidence of this occurrence however has been greatest in patients who have been treated with the so-called wide spectrum antibiotics The most frequently encountered gastrointestinal symptoms are nausea, vomiting, diarrhea and pruritus.

The nausea and vomiting which has been observed during the use of these antibiotics have been attributed to a variety of causes First there are those who believe that the irritating action is due to some direct effect upon the stomach However examination of the stomach by x rays or gastroscopy usually has revealed no significant structural changes in the largest number of these cases. Avoidance of nausea has been reported as being significantly reduced by giving milk with each dose of the drug For a time the concomitant use of aluminum hydroxide and the simultaneous administration of acidophilus milk, was felt to be ameliorative The use of aluminum hydroxide however should be discouraged, in view of the fact that it has been shown to interfere with the absorption of chlortetracycline with the result that the blood level of this antibiotic is significantly less when this agent is used in an effort to reduce nausea Occasionally a true gastritis may result from

the use of some of the broad spectrum antibiotics However such cases are rare

Diarrhea, accompanied by cramps and tenesmus continues to be an important and distressing complication attending the use of the broad spectrum antibiotics The incidence of its occurrence following chloramphenicol administration, however appears to be less than that seen when chlortetracycline and oxytetracycline are used. Diarrhea may begin after a single dose but more often is seen after three or four days of therapy Occasionally the diarrhea persists for weeks or even months after therapy has been discontinued. Many explanations have been offered to explain the diarrhea which is seen as a result of antibiotic therapy Of these direct irritative effects by the drug drug allergy vitamin B complex deficiency and changes in the intestinal flora are noteworthy While direct irritation by the drug may be a factor in those cases in which diarrhea is seen following a few doses of antibiotics the consensus appears to favor the view that the diarrhea is in one way or another related to changes produced in the intestinal flora These changes have been reported to be of two kinds first a marked reduction in total numbers of some of the fecal bacteria which are common to the gastrointestinal tract. Secondly there is a change in the qualitative composition of the bacterial flora. However this shift, both quantitative and qualitative, persists for only a few days and upon continuation of therapy there appears to be a reestablishment of the original bacterial flora. In some cases there has been noted an increase in the number of *Candida albicans* organisms in the stool. There are reports that Proteus as well as staphylococci also seem to increase in numbers following wide spectrum antibiotic therapy It has been speculated that these bacterial changes cause al

tered intestinal motility either as a result of chemical irritation or by proliferation of mildly pathogenic organisms which suddenly find themselves devoid of inhibiting antagonists It is clear however that the basic mechanism remains obscure especially when one considers that the diarrhea may persist for a long time after the drug has been withdrawn and also that when neomycin alone or in combination with other drugs is used preoperatively as a gastrointestinal preparative measure there is a very low incidence of diarrhea associated with its use although the drug is very effective in eliminating most of the bacteria.

Ulcerative proctitis and colitis have been reported in individuals receiving antibiotics. In some of these cases the lesions are indistinguishable from nonspecific ulcerative colitis. It is for this reason that the management of patients with ulcerative colitis by means of antibiotic therapy should be approached with caution, particularly when it is decided to use wide spectrum antibiotics. A very important bowel complication which more recently has been increasing in frequency is the so-called pseudomembranous colitis This condition is characterized by severe diarrhea, attended or followed by a shock like picture, and, in some instances death is alleged to have occurred in a few days In a number of these cases the lesion appears to be due to a staphylococcus. When this condition has been reported, usually patients have received either chlortetracycline, oxytetracycline, and combinations of penicillin and dihydrostreptomycin. There are on record a few cases in which this condition has occurred and in which no antibiotics were used. One should bear in mind that when the disease is suspected of being caused by a staphylococcus the efficacy of erythromycin for this type of organism, should be kept in mind.

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Ulcerative proctitis and colitis have been reported in individuals receiving antibiotics In some of these cases the lesions are indistinguishable from nonspecific ulcerative colitis. It is for this reason that the management of patients with ulcerative colitis by means of antibiotic therapy should be approached with caution, particularly when it is decided to use wide spectrum antibiotics A very important bowel complication which more recently has been increasing in frequency is the so-called pseudomembranous colitis This condition is characterized by severe diarrhea, attended or followed by a shock like picture and, in some instances death is alleged to have occurred in a few days In a number of these cases the lesion appears to be due to a staphylococcus When this condition has been reported usually patients have received either chlortetracycline oxytetracycline and combinations of penicillin and dihydrostreptomycin There are on record a few cases in which this condition has occurred and in which no antibiotics were used One should bear in mind that when the disease is suspected of being caused by a staphylococcus the efficacy of erythromycin for this type of organism should be kept in mind

Pruritus ani is another very common complication which follows the use of certain broad spectrum antibiotics and which may persist for months. Here, as in diarrhea, the responsible mechanism is obscure. It has been suggested that, as in stomatitis and diarrhea, vitamin B complex deficiency associated with alteration in normal bacterial ecology is the underlying cause. It is suggested that meticulous hygiene be observed during antibiotic therapy to reduce the incidence of this complication. When it does occur the administration of yogurt or lactic acid bacilli has been reported as helpful. Occasionally local applications of gentian violet may be used, if the condition is felt to be due to a moniliasis More recently local application of hydrocortisone, in ointment, has been suggested.

A sub-group entity presently suspected of being a complication of antibiotic therapy and discovered by workers using the needle biopsy technic, consists of the finding of fatty changes in the livers of patients who are receiving chlortetracycline or oxytetracycline These changes are reversible and usually disappear very soon after the drug is discontinued Increase of urinary nitrogen accompanies these changes and in isolated patients there have been reports that a negative nitrogen balance may actually develop Methionine appears to be ineffective in the reversal of these fatty changes

While the gastrointestinal complications attending the use of antibiotics are annoying they are usually not serious The use of undecylinic acid has been advocated as an agent for controlling monilial complications secondary to the use of the tetracyclines and chloramphenicol. Recommended dosage is 0 44 Gm. orally concurrently with the use of each 250 mg capsule of antibiotic. It is claimed that this agent does not interfere with the therapeutic qualities of the anti-

biotics However undecylinic acid does not appear to de crease the incidence of severity of diarrhea nor prevent the appearance of bacterial opportunists, like Proteus pseu domonas or staphylococci. More recently Mycostatin (Ny statin E R Squibb & Sons) has been introduced as an agent for the prevention and management of gastrointestinal monil iasis It is available as 500 000 unit tablets to be given t. i d When taken by mouth it is not absorbed and is stated to be compatible with all the present orally administered anti biotics. Up to the present time no serious toxic effects have been reported even with large doses administered for weeks Additional clinical experience is required before it will be possible to accurately assess the clinical value of this drug

GENITOURINARY COMPLICATIONS

There are several untoward reactions or complications associated with the chemotherapy of genitourinary infections. First, there is vaginitis, a condition which is most frequently seen in patients treated with wide spectrum antibiotics. Second, obstruction in the urinary tract, or crystalluria, may be seen in patients receiving sulfonamides for long periods of time. Third, the development of antibiotic resistance may occur in those instances where antibiotic agents are used indiscriminately and for relatively long periods of time without evidence of the identity of the organism in volved in the infection. Fourth, cholera like symptoms associated with the presence, or overgrowth, of penicillin resistant staphylococci in the bowel may develop Fifth, there may be direct toxicity due to the agent itself as for example polymyxin and the nephrotoxicity associated with its use.

Among urologists, it is not infrequent to see an increasing number of patients with monilial vaginitis and irritation

around the urethral meatus Usually this begins several days following the initiation of antibiotic therapy These patients come to the urologist with the principal complaint of burning on urination as the predominant symptom This complication occurs very frequently in elderly ladies past the menopause, who have an atrophic vaginal epithelium.

During the time when the sulfonamides first came into wide use many patients receiving these drugs complained of oliguria and anuria, which were subsequently shown to be due to precipitation of sulfonamide crystals into the urinary tract. The diagnosis is not difficult to make since these patients are usually taking large doses of the drug, are not forcing fluids and are not alkalinizing the urine. Most often, cystoscopy will reveal clusters of yellow crystals projecting from both ureteral orifices Occasionally there will be additional precipitation within the collecting tubules and renal parenchyma and still more rarely there is a nephrotic type of reaction of the renal tubules. As a result of these observations there have been developed sulfonamide drugs whose solubility in urine of normal *p*H is greatly increased over and above that which is characteristic for the sulfonamides first introduced. Sulfadiazine when used should be given in combination with an alkalizing agent, such as sodium bicarbonate However within recent years more soluble sulfonamide drugs, such as gantrisin and elkosin and the so-called triple sulfonamide mixtures, are becoming more acceptable despite the fact that among clinicians there is a feeling that sulfadiazine is a more potent antibacterial than either gantrisin or elkosin It is important to emphasize the necessity of forcing fluids during the administration of sulfadiazine

In preparation of ureterosigmoid transplantation it is a commonly accepted practice to administer antibiotics or

sulfonamides in an effort to sterilize the bowel so that any fecal material spilled at surgery will do minimal damage in the peritoneal cavity For this purpose tetracycline oxytetra cycline bacitracin neomycin or sulfathaladine have been used. While there have many cases where this method of preoperative bowel preparation have been unattended by undesirable sequellae there have been a few instances where this practice of sterilizing the bowel has occasionally resulted in a fatal complication It seems that some patients harbor a staphylococcus which is resistant to the sterilizing antibiotics used and, as a result of the removal of the associated fecal flora, it undergoes a tremendous overgrowth in the bowel. Such patients develop an overwhelming staphylococcal tox emia and septicemia and a few reports of death have been the result. Awareness of this possibility cannot be overempha sized and when indications appear which would lead one to suspect initiation of an overgrowth of staphylococci it is well to remember the specific action of erythromycin against these organisms

In the treatment of renal tuberculosis a serious disease often requiring at least one year or more of therapy it should be remembered that the various agents used for the treatment of this disease may give rise to complications Ataxia, resulting from protracted use of streptomycin, is not nearly so much of a problem today as it was in the days when streptomycin was given daily Dysfunction of the vestibular auditory apparatus as a result of either strepto- mycin or dihydrostreptomycin alone for the treatment of this disease, would appear to be considerably reduced when one employs a combination consisting of one half strepto- mycin and one half dihydrostreptomycin In view of the fact that drug resistance to streptomycin develops rather rapidly it is important that patients wih renal tuberculosis

be given *streptomycin in conjunction with PAS or isoniazid.* The same is true of isoniazid. In other words neither streptomycin nor isoniazid should be given alone they should always be given in combination with PAS Isoniazid is a central nervous stimulant, in addition to possessing anti tuberculous activity If it is given to patients whose renal function is severely damaged by tuberculosis the blood level will rise progressively as the drug accumulates in the blood stream as a result, the patient will begin to show neurologic manifestations consisting essentially of nervousness and jitterness This may be followed by sphincter spasm requiring banthine to enable him to void, and finally the patient may even develop a hyperreflexia, convulsions, and possibly die Therefore, it is important to remember that in patients who are moderately uremic as a result of destructive tuberculosis of the kidney it is necessary to decrease the dose of insoniazid to approximately two-thirds that which is usually used in patients with other forms of tuberculosis. The use of polymyxin in patients with urologic manifestations should be approached with care in view of the recognized nephrotoxicty of this antibiotic

PULMONARY COMPLICATIONS

Pulmonary complications attending the use of antibiotics can be grouped into three major classes (1) Allergic re*actions* (2) *development* of bacterial resistance to anti biotics and (3) infections occurring secondary to anti biotic therapy

At the present time allergic reactions to parenteral ad ministration of penicillin represent the most serious hazard of antibiotic therapy It has been reported that the inci dence of sensitivity to this antibiotic is in the

of about ten per cent. The allergic responses that have been seen following the use of this antibiotic include Anaphylactic shock and death, urticaria, periarteritis nodosum, and exfoliative dermatitis Unfortunately these reactions cannot be safely and universally predicted or prevented, either by penicillin skin tests or by the use of hypoallergenic penicillin such as penicillin O In many allergic reactions to penicillin the employment of an antihistaminic agent can be extremely helpful

Anaphylactic shock, due to penicillin may include severe bronchial spasm and edema When this state occurs it involves the emergency use of a number of measures Among these are artificial respiration the administration of oxygen or helium-oxygen mixtures pressure breathing, and intubation, including intravenous injection of 1 1000 adrenalin, or some antihistaminic and ACTH by infusion are helpful. When pulmonary edema is present intermittent pressure breathing is indicated.

In view of the relatively high incidence of penicillin sensitive individuals, there seems to be a trend developing toward the reservation of parenteral penicillin to those cases in which exceptionally high blood levels of the drug are required for survival. There are those who feel that for the minor ailments in which penicillin is indicated, the oral preparations are preferred, in view of the fact that the incidence of serious reactions to penicillin administered by mouth has been shown to be negligible in comparison to that seen with parenteral penicillin. The introduction of dibenzylethylene diamine penicillin (DBED) which may be given following meals without a decrease in blood level such as is seen when crystalline penicillin is given under the same conditions has made available a useful drug to diminish the incidence of sensitivity to penicillin in patients.

Another complication of penicillin seen in patients is red and black tongue which is associated with oral administration, or the inhalation of nebulized, penicillin. This manifestation of toxicity may be prevented by using penicillin in capsule form, or as a coated tablet. It may be prevented also at least in part, by washing the mouth and drinking water after treatment. Red and black tongue is not peculiar to oral penicillin, but may also be seen where the drug is used systemically In patients with bronchial asthma and pulmonary emphysema, who may be treated by inhalation therapy of penicillin aerosol, allergic reactions which are seen in approximately twenty per cent of these patients, are not due to allergy but to the effect of the physical impact of the mist. Aerosol therapy with penicillin is especially indicated in cases of bronchiectasis and suppurative sinusitis

Development of bacterial resistance and infections secondary to antibiotic therapy are closely associated and will therefore be discussed together In bronchopulmonary infections *Staphylococcus aureus* is the chief organism which has been shown to develop a significant resistance to antibiotics and there is no longer any question that the incidence of penicillin resistant staphylococci, particularly in hospitals, is today considerably higher than it was when the antibiotic was first introduced into general use With out attempting to discuss the various mechanisms which explain this high incidence of penicillin resistance of staphylococci in hospitals suffice it to say that it is not an unusual occurrence today to find that only twenty per cent of staphylococci which are isolated from clinical specimens are sensitive to penicillin. A similar trend with respect to the other antibiotics has been observed and also seems to be associated with the increased frequency with which a

particular antibiotic is used or given in the institution It is for this reason and particularly amongst the staphylococci that studies of the sensitivity of the organisms from the sputum have become almost a necessity In bronchiectasis where the involved organisms may include the staphylococci it is felt that current treatment should consist of at least one million units of penicillin daily In view of the fact that many penicillin resistant staphylococci are still found to be susceptible to tetracyclines and erythromycin it is important to keep these agents in mind when penicillin appears to be ineffective assuming of course that sensitivity studies have indicated that these agents are effective In cases of penicillin resistant staphylococci, which have become resistant to erythromycin or tetracycline it may be necessary to resort to intramuscular injection of streptomycin combined with the administration of large doses of penicillin by mouth

Infection of the bronchi or lungs with bacterial opportunists, such as monilia, Proteus Klebsiella, and Pseudomonas organisms has taken place as a result of the administration of large doses of wide spectrum antibiotics as well as penicillin especially when the former agents are given over a long period of time or to debilitated patients. When these organisms are found in sputum in patients who have received antibiotic therapy it is important to differentiate whether the observed organisms are actually involved in the infection or whether they represent manifestations of organisms which were originally present, but whose appearance was made manifest only after the destructive effect of the initial therapeutic agent on the associated flora. When these organisms are felt to be truly involved in the infection, it is well to remember that *in vitro* sensitivity tests are not infallible and although such tests may indicate these organ

isms to be resistant to the various agents, there are on record cases where clinically good results have been obtained with the use of such agents as chloramphenicol, streptomycin, and intensive penicillin.

There seems to be a realization developing that antibiotic agents in general are extremely potent therapeutic tools and that in the past there has been a tendency to use excessively high dosages Within recent years, there has been a tendency towards smaller dosages, with, apparently no sacrifice in therapeutic results

Unfortunately there can be no hard and fast rules set down upon which one can rely in every case for the successful treatment of chronic bronchopulmonary infections However this appears to be generally accepted First, penicillin is the drug of choice for infections in which gram positive organisms are involved. Second, oral administration of penicillin in dosages of one million units on an empty stomach, two or three times a day should be used in place of parenteral injections where possible. Third, the concomitant use of an antihistaminic drug is indicated when intramuscular injection is given, and probably also in a small percentage of allergic patients who are receiving the drug orally Low dosage of the wide spectrum antibiotics is preferable to high dosage administered briefly Fourth, the recently developed physical methods of accomplishing bronchial drainage should receive noteworthy consideration. Adequate drainage of retained pulmonary secretions may be aided by other measures such as the use of the head-down position and bronchodilator aerosols.

The antimicrobial agents may so modify the disease as to confuse the diagnosis As a result, we are seeing an increasing number of patients in whom the classical signs and symptoms of the disease are masked or modified by

these drugs, notably syphilis mastoiditis, and localized in flammatory lesions in the abdomen For this reason it is sometimes advisable to discontinue all antimicrobial ther apy in those patients in whom the response has been un satisfactory and in whom the diagnosis is uncertain Not only does this give the disease an opportunity to manifest itself more definitely but also eliminates the possibility of drug toxicity

DRUG RESISTANT INFECTIONS

The widespread and indiscriminate use of the antimicrobial agents has resulted in an increased number of drug resistant bacteria This increased microbial resistance fol lowing exposure to an antibiotic not only holds for the antibiotic itself but also the possibility of the development of cross resistance to other antibiotics exists In considering this problem of drug resistant infections one must distin guish between the natural and the acquired resistance of microorganisms. Natural resistance or susceptibility to these agents varies widely among bacterial species as well as among different strains of a given species. Acquired re sistance for the most part results from continued exposure to sub-inhibitory concentrations of these drugs The development of resistance to streptomycin often occurs within a period of a few days whereas very few organisms become resistant to penicillin It is true that the incidence of peni cillin resistant staphylococcic infections has increased rapidly over a period of years (approximately twenty per cent in 1943 to seventy five per cent in 1952 in hospital infec tions) but it is thought that this is due to the reduction in the number of naturally sensitive strains thereby giving the naturally resistant strains already present an opportunity to become predominant.

More recently Julius has enunciated a concept relative to drug resistance which permits realistic appreciation of the problem and raises the question as to whether it will ever be possible to find antimicrobic agents that will not induce resistance. An antimicrobic agent to possess specific killing properties must be presumed to have the capacity to interfere with some part of a function which is vital to living organisms (parasites) but not vital to the host. In both instances such a function, or bypath must be more or less remote from the most fundamental features of life itself. This immediately implies the possibility for bypassing the function and, once this is realized, regardless of the manner of its occurrence, there will be resistance. In other words, *a substance incapable of inducing resistance would seem to* have little chance for possessing antimicrobial activity.

"Because some of the bacteria have the power of making themselves resistant to all antibiotics it is essential that drugs should not be abused. That is difficult in these days of newspaper publicity."

Sir Alexander Fleming (May 21, 1953)

SUPERINFECTIONS

Statistics show that there has been a definite decline in the number of patients suffering with infectious diseases in this country during the past 100 years. No doubt, such factors as improvement in general nutrition and hygiene, better housing, improvement in food handling and in water supply, the decline in virulence of infecting organisms, and increased resistance to infections have singly or in combination been responsible for these results. The question naturally arises as to the influence of antimicrobial therapy upon the relative incidence of infectious diseases. Unfortunately the wide therapeutic range of the antimicrobial agents has resulted in a failure in most instances to

establish an etiological diagnosis Usually the necessary laboratory studies are reserved for cases failing to respond as anticipated to the initially prescribed therapy For this reason accurate figures dealing with the treatment of large groups of infectious diseases are becoming increasingly dif ficult to assemble and as a consequence, data regarding the newer antibiotics are limited Diseases such as gonorrhea and syphilis with established etiologies and with effective measures for prophylaxis and treatment are definitely on the decrease Such conditions as classical pneumococcic pneumonia are certainly diminishing in frequency in hos- pital practice while there is an increasing proportion of infections due to gram negative bacteria In addition more cases due to rickettsiae fungi and protozoa are being seen. This apparent increase of infections due to the latter group of agents may well be the result, at least in part, of the introduction of new and more specific laboratory diagnostic methods Nevertheless the importance of the effect of antimicrobial therapy upon the indigenous bacterial flora of the body is gradually but certainly being recognized. Normally the body harbors many organisms which in small numbers are not pathogenic relatively avirulent, and cause no symptoms. When the normal ecology or microbiological balance is disturbed by antimicrobial therapy such organ isms may increase in numbers and invasiveness and give rise to infections Occasionally infections with micro-organisms usually regarded as non-pathogenic, will occur during antibiotic therapy and prove to be insensitive to the drug being employed. Such superinfections result from the dislocation of the normal bacterial flora of the sino-respir atory gastrointestinal, and genitourinary tracts Several mechanisms to explain these superinfections have been pos tulated (a) Administration of an antibiotic results in virtual

elimination of susceptible organisms thus reducing the numbers competing for available food supply The resistant *organisms then vastly increase in numbers and overwhelm* the host s resistance (b) Normal flora supplies certain nutritional requirements of the host. Disturbance in the normal flora results in a nutritional disturbance which modifies the integrity of the mucous membranes, thereby opening a portal of invasion to organisms which normally are unable to penetrate the healthy mucosae. (c) Some antibiotics such as chlortetracycline, are suspected of directly stimulating growth and virulence of *C albicans* with the ultimate production of candidiasis The superinfections when they occur are not correlative with the use of any one antibiotic. Evidence exists to indicate that penicillin as well as chloramphenicol, and the tetracyclines may be involved. Hence, the importance of bacteriological studies to follow the changes in bacterial flora in various regions of the body in patients being treated for infectious diseases

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Diagnosis of Infectious Diseases

Early Diagnosis

The length of time that elapses between the onset of the infection and the beginning of treatment is not necessarily of prime importance except in those more serious diseases involving the blood stream, the meninges and the endocardium Nevertheless one should institute therapy as soon as the clinical diagnosis has been made and the necessary material has been collected for laboratory study In many cases of infectious disease it is impossible to be sure of the diagnosis when the patient is seen for the first time. Although antibiotic therapy need not be withheld until a bacterial diagnosis has been established, there are occasions when it is justifiable to wait for further developments in order to arrive at a more accurate diagnosis or to see if the condition will not improve spontaneously Today however with the widespread use of antibiotics the physician often finds it difficult to withhold these "miracle" drugs at the time of his initial visit. The patient demands relief and the relatives are insistent that something be done. To succumb to these pleas is often literally a fatal mistake since these therapeutic agents may so modify the disease as to confuse the diagnosis

Accurate Diagnosis

The dramatic effectiveness of the antimicrobial drugs is responsible for a definite trend towards carelessness in clinical diagnosis and an apparent disregard for the need of adequate laboratory studies Obviously there are many infections which respond dramatically to antibiotics without benefit of an accurate diagnosis In some instances the causative organism can be accurately recognized without laboratory aid by virtue of the characteristic clinical picture of the disease. In others however the diagnosis is to a large extent one of exclusion and in these cases it is often necessary to accumulate considerable clinical, laboratory and x ray data. It is in this group that the proper battery of laboratory tests together with an adequate history and physical examination aid greatly in establishing an accurate diagnosis

Etiological Diagnosis

The unequivocal determination of the causative agent is one of the more important factors in the successful management of infectious diseases Unfortunately the rather wide antimicrobic spectrum of antibiotics has resulted in a failure in most instances to establish an etiological diagnosis Usually the necessary laboratory studies are reserved for cases failing to respond to therapy For this reason, exhaustive data dealing with the treatment of large groups of infectious diseases are becoming increasingly difficult to assemble. Despite this certain patterns have developed which indicate that certain groups of bacteria are more easily controlled by different antibiotics For example certain strains of Klebsiellae are more sensitive to chlortetracycline than to streptomycin Many strains of staphylococci are resistant to penicillin but will respond to erythromycin and the

tetracyclines. Typhoid infections are best treated with chlor amphenicol. Not infrequently a unique situation exists wherein an antibiotic with a limited range of activity is the best drug for an infection, such as polymyxin in pseudomonas infection In other words, successful antibiotic ther apy is becoming a more specific form of treatment and depends to a certain degree on specificity of action—hence, the importance of knowing the causative agent in each in fection in order to administer the most suitable antibiotic Theoretically this should be done routinely but from a practical standpoint, is frequently difficult to carry out. Therefore there must be some middle road between the practice of giving antibiotics indiscriminately to everyone with an elevation in temperature and that of withholding antibiotic therapy until a definite diagnosis is established. Certainly all serious infections such as those involving the blood stream, the meninges the endocardium and those infections which fail to respond satisfactorily demand efforts on our part to establish an etiological diagnosis

After the causative organism has been isolated and identi fied, antibiotic therapy can be selected intelligently for most infections without resorting to sensitivity tests provided there is an awareness of the comparative antibiotic sus ceptibility of groups of bacteria and the pharmacology of the antibiotic agents. The need for specific susceptibility testing is more critical when dealing with organisms dif ferent strains of which are known to exhibit wide variation in individual antibiotic susceptibility It appears to be gen erally true that strains of gonococci pneumococci, and group A hemolytic streptococci are quite uniform in their susceptibility to a given antibiotic Other organisms such as staphylococci, enterococci and gram negative urinary tract pathogens differ widely in their antibiotic sensitivity

Although the determination of bacterial sensitivity to antibiotics is a widely employed procedure, its results may be misleading to the physician unless properly interpreted. The usefulness of these tests is based on the assumption that the effectiveness of the various chemotherapeutic agents as seen in *in vitro* tests parallels the therapeutic results *in vivo* and, *while such an assumption may be valid* for the most part, there are exceptions. Clinical results are of course, influenced by the degree and extent to which the particular antibiotic is distributed in the body and it is not an uncommon experience to find that the clinical effectiveness may differ from the results reported in *in vitro* tests. In this connection, the clinical activity of penicillin is especially likely to be underestimated in *in vitro* tests. Infections due to a strain only slightly susceptible to concentrations of penicillin employed in laboratory tests may clinically respond rapidly to penicillin because of the uniformity of blood and tissue concentrations readily maintainable *in vivo* with the drug. In general, it is wise to consider results of sensitivity tests as determined routinely in most laboratories *solely as qualitative guides to distinguish susceptible* from nonsusceptible organisms and to select the antibiotic to be used on the basis of location of infection in relation to drug pharmacology and state of the patient.

In order to provide more rapid information to the physicians, we are employing the following routine in our laboratory. Organisms are tested by disk for inhibition by or lack of it to penicillin, streptomycin, erythromycin, chloramphenicol, and the tetracyclines at the concentration equivalent to blood concentrations easily obtained by moderately intensive chemotherapy. Results are reported in terms of sensitive or resistant. An organism found resistant to any of these agents by these methods is studied

by serial tube dilution for more quantitative determination of inhibiting concentration. Because of the uniform high susceptibility of streptococci (enterococci excluded) pneumococci *H influenzae* and Neisseriae these organisms are not tested routinely for response to antibiotics However all staphylococci enterococci coliforms *Shigellae Proteus Salmonellae* and *Klebsiellae* organisms are studied. In addition all organisms isolated from cases of subacute bacterial endocarditis are tested for penicillin streptomycin and erythromycin sensitivity by serial tube dilution technic

In addition to the above, bacteriological studies show that the physician must be familiar with the progress which continues in the field of infectious diseases and that new types and new distribution of etiological agents are calling for new diagnostic methods. Not only must the material for study be collected properly but such information as the stage of the disease or duration of illness pertinent signs and symptoms and the type of therapy being employed should be recorded also

Clinical Diagnosis

The diagnosis of infections cannot be made solely from laboratory studies It remains for the physician to determine the etiology not only from these findings but from a detailed history and careful physical examination

History Taking

One of the most important steps in arriving at a diagnosis is to recognize and note the earliest symptoms of the disease. Not infrequently a properly taken history will narrow the diagnostic search to a few important diseases It is for this reason that the general practitioner is in an enviable position to record such facts before starting chemo-

therapy which greatly adds to the stock of common knowledge Today because of the wide therapeutic effectiveness of the antimicrobial agents most infectious diseases are treated successfully at home. No doubt, the accuracy of future medical literature dealing with infectious diseases will depend largely upon those who see the patient initially and record not only the disease but the action of the drugs employed. Therefore the importance of a thorough history cannot be overemphasized. Not infrequently valuable information pertaining to the patient's illness can be elicited, not only from the patient, but from other members of the family Today we are often too busy to take a detailed history before starting treatment.

Physical Examination

It has been said facetiously but with some degree of truth, that if a patient does not improve after forty-eight hours of antimicrobial therapy a physical examination should be performed. Certainly no patient should receive any therapy without first having a thorough physical examination. It is true that not infrequently the only abnormal physical finding in a case of infectious disease is that of fever However this does not excuse the physician from thoroughly examining all parts of the body for possible diagnostic clues Although the common denominator in systemic infections is fever it does not follow that all fevers are due to infection, although in this chemotherapeutic age there is a growing tendency to treat all fevers as such until proven otherwise. If perchance the therapeutic test is unsuccessful, then one is confronted with the problem of arriving at an accurate diagnosis It is in this so-called failure group that we meet most of our diagnostic problems today Fortunately however most infections, if untreated,

will sooner or later give rise to characteristic symptoms physical findings or abnormalities of laboratory tests which taken singly or together will point the way towards an accurate diagnosis There are probably fewer cases of fever of undetermined etiology since the advent of modern therapy because many infections are eradicated by these agents without their exact location or nature being known As mentioned previously recognition of most infectious diseases is not difficult since in many instances the causative organism can be accurately recognized without bacteriological proof by virtue of the classical clinical picture resulting from the infection. Here again is a demonstration of the importance of recognizing and recording the early signs of the disease

Failure to examine the throat is a glaring sin of omission, especially in children. One finger in the throat and one in the rectum makes a good diagnostician.

Sir William Osler (1849–1919)

FOCI OF INFECTION

The problem of focal infections represents one of the most important factors in the treatment of patients suffering with infections The concept of focal infection in relation to systemic disease is now firmly established Any localized infection is potentially a focus from which bacteria, their toxins or other dissoluted products may at any time, spread *via* the contiguous tissues blood stream, and lymph channels to induce an infection in communicating or distant tissues or to sensitize them. No doubt such factors as overfatigue, malnutrition anemia, and preexisting tissue damage elsewhere in the body play important roles in the development of systemic infections from such foci Furthermore the treatment of certain diseases with ACTH and cortisone

indicates that alterations in physiological phenomena also play an important part It is unreasonable to expect, therefore that the removal of focal infections will eliminate a well established disease process which is characterized by fibrosis or tissue necrosis Nevertheless it is important to obtain an accurate history and to perform a careful physical examination in hopes of detecting a possible focus of infection. Certainly a history of recurrent bouts of furunculosis, diarrhea, deafness running ear or a recent tooth extraction, as well as many other leads will often be helpful in this regard. Undoubtedly many potential or established foci of infection may and can be successfully eradicated with the use of the antimicrobial agents alone. For this reason many unrecognized foci of infection are eradicated without their exact location or nature being known. On the other hand, it should be remembered that antimicrobial agents may modify a disease so as to confuse its diagnosis so that at present we are seeing an increasing number of patients in whom the classical signs and symptoms of disease are masked or modified by these drugs In other instances, the nature of the disease process is such that these drugs are relatively ineffective. It is in this last group particularly that every effort must be made to detect and eradicate the focus of infection. Thus keeping in mind the fact that regardless of the proven prophylactic and therapeutic effectiveness of the antimicrobial agents, they are not to be used to the exclusion or neglect of other proven forms of therapy

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Antimicrobial Therapy of Specific Infectious Diseases

SUPPORTIVE TREATMENT IN INFECTIOUS DISEASES

REGARDLESS of the proven value of the chemotherapeutic agents they are not to be used to the neglect or exclusion of established supportive forms of therapy

Rest in Bed

Not only does the recumbent position lessen malaise and relieve the sense of fatigue, but the work of the heart, kidneys and liver is reduced Blood flow to the kidneys and liver tends to be greater in the recumbent position. When the patient is ready to resume activity he should be allowed to do so gradually Bed rest has certain disadvantages namely diminished respiratory excursions which may lead to atelectasis and a sluggish blood flow predisposes to phlebothrombosis in the lower extremities Furthermore prolonged confinement may have an unfavorable psychological effect on the patient.

Nursing Care

Good nursing care is often the difference between success or failure in certain serious illnesses Patients must be turned from side to side at frequent intervals and encouraged to take

deep breaths The sheets should be dry and free of wrinkles The fluid intake must be overseen. Hygienic measures such as mouth washes and cleansing of the lips teeth, and tongue must be carried out. Frequent change of bedding and night clothes where profuse sweats occur is essential.

Diet

In many febrile illnesses of short duration, diet is of little importance whereas in a prolonged febrile illness it constitutes a very important factor in the patient's recovery The utilization of vitamins and foods rich in proteins and carbohydrates has a role in the patient's recovery

Fluid Intake

During fever there is increased loss of water vitamins, calories and electrolytes so that it is necessary to replace these essentials When this cannot be done by mouth, it is necessary to resort to parenteral therapy

Care of Bowels and Bladder

Fecal impactions gaseous abdominal distentions, and overfilled bladders constitute real handicaps in the recovery of a seriously ill patient. Hence, the importance of measures to prevent and alleviate the same namely mineral oil, enemas rectal tubes application of hot turpentine stupes or flaxseed poultices the use of pituitrin like drugs, and early catheterization

Symptomatic Treatment

When the temperature becomes very high, above 104 F (40 C) or when delirium is present, attempts should be made to reduce the fever The use of antipyretics such as acetylsalicylic acid, and sponging with alcohol are both

useful. In addition febrile illnesses are often accompanied by headache, photophobia, sleeplessness etc and in such cases the use of cold compresses or codeine darkening the room and the use of barbiturates is often helpful

ANTIMICROBIAL THERAPY OF SPECIFIC INFECTIOUS DISEASES

Sinorespiratory Tract Infections

Infections of the respiratory tract are encountered more often than any other group of diseases in the practice of medicine Although modern antimicrobial therapy has reduced the morbidity and mortality in a spectacular manner in many types of respiratory tract infections this group of diseases as a whole still represents a real challenge, especially the management of certain chronic bronchopulmonary diseases

The Common Cold

At this time more patients receive antimicrobial agents for the common cold, coryza, than for any other disease although as yet none of these agents has been unequivocably demonstrated to have a favorable effect in the treatment or prevention of the uncomplicated common cold. The reasons for this indiscriminate practice are the belief that such measures will prevent the development of secondary bacterial infections plus the physician's and patient's urge for specific therapy in place of supportive measures Hence the routine use of these agents for the treatment or prevention of this disease does not seem warranted. However in cases in which bacterial complications are present, or where past experience would suggest that they may occur in certain individuals or during periods in which there is a high prevalence of infections due to susceptible bacteria, one is

justified in employing one of these agents Since the infection is often a mixed one therapy with a wide spectrum antibiotic seems indicated (tetracycline or oxytetracycline, orally 250 mg every six hours) or in cases where gram positive organisms are the chief offenders, penicillin by mouth, 250 000 units every six hours Additionally erythromycin 200 mg orally every four to six hours may be used effectively

Ozena

The question of bacterial origin in ozena is still unsettled, although *Klebsiella* organisms are frequently found. While favorable results have been reported following the use of streptomycin, 1 Gm daily for ten to fourteen days, recurrences are frequent.

Sinusitis—Otitis Media—Mastoiditis

Although antimicrobial therapy has frequently eliminated the necessity of surgical interference in the successful management of acute infections of the paranasal sinuses middle ear and mastoids the fact remains that adequate drainage, either by the creation of an adequate nasal passageway by use of suitable agents, or surgical attack, constitutes the essentials of therapy Supplemental antimicrobial therapy nevertheless plays a important role in the medical and surgical management of such cases.

Most acute sinus infections represent but part of a generalized upper respiratory tract infection which is viral in origin and is not influenced by antimicrobial therapy However when the exudate becomes purulent, it usually indicates a bacterial infection and antibiotic therapy should be instituted. Most of these infections are due to one of the gram-positive bacteria and penicillin is usually effective. In

general procaine penicillin, 300 000 to 600 000 units daily for five to ten days and longer if necessary or in severe cases aqueous penicillin G 200 000 units every three to four hours are recommended In view of the potential intracranial complications, it is advisable to carry out careful sensitivity studies on the infecting agent, or agents as a mixed infection or a penicillin resistant organism calls for a wide spectrum drug (tetracycline or oxytetracycline 250 to 500 mg. every four to six hours)

Otitis Media

Most cases of acute otitis media are due to streptococci with pneumococci and staphylococci next in frequency Once the diagnosis is made, constant observation is indicated and the presence of increasing pain, elevation of temperature and evidence of fluid or bulging requires more than symptomatic therapy In such cases incision of the tympanic membrane and antimicrobial therapy are indicated. No doubt, many cases will respond to antibiotic treatment alone, but in our experience the acute otitis media which requires drug therapy also requires drainage Procaine penicillin 300 000 to 600 000 units daily for four to seven days is usually sufficient, although sensitivity studies may reveal that tetracycline or oxytetracycline 250 to 500 mg. every four to six hours is indicated.

Mastoiditis

Most cases of acute mastoiditis are secondary to infections in the middle ear and the treatment is essentially the same as outlined above for acute otitis media. Close clinical, ostoscopic, and x ray observation is extremely important in this disease, in that the masking effect of the antibiotics will at times confuse the picture and intracranial complica

tions may develop This is particularly true in acute mastoiditis associated with certain meningeal infections, especially pneumococcal meningitis

Pertussis

Although certain of the antimicrobial agents are effective against *H pertussis in vitro* the fact remains that once the infection sets in, the elimination of the causative agent does not greatly affect the course of the disease Nevertheless, the early administration of one of the wide spectrum antibiotics tetracycline or oxytetracycline 50 mg kg. body weight in divided doses every four to six hours, for five to seven days may reduce the severity of the infection. Penicillin is indicated in the treatment of some complications

Acute Pharyngitis and Tonsillitis

The type of acute pharyngitis most frequently encountered is that associated with the common cold It is not amenable to treatment with the antibiotics and is best handled by local therapy with hot saline gargles. In contrast to this type of sore throat is pharyngitis due to the streptococcus, which is characterized by systemic toxicity and, regardless of the severity the patient should receive antibiotic therapy preferably penicillin, orally 250 000 units every four to six hours or procaine penicillin 300 000 to 600 000 units daily for five to seven days Erythromycin 200-400 mg orally every four to six hours or tetracycline or oxytetracycline 250-500 mg. orally every four to six hours may be used effectively

Acute Laryngotracheobronchitis

Acute infections involving the larynx, trachea, and/or bronchi are in themselves usually mild and of short duration. However there is always the danger of the infection extend

ing into the lung parenchyma causing pneumonia, especially in infants and debilitated or elderly patients with pre-existing pulmonary or cardiac disease Although the infection is often preceded by a common cold many cases begin directly with a pyogenic infection due to one or more organisms such as streptococci, pneumococci staphylococci or *H influenzae* Since the infection is often a mixed one, therapy with a wide spectrum antibiotic is indicated Tetracycline or oxytetracycline 250 to 500 mg. every four to six hours

PULMONARY INFECTIONS

Pneumonia

Pneumonia is no longer considered a single disease entity but rather as a group of specific infections with a common denominator namely an exudative inflammation involving one or more lobes of the lung In general, pneumonias may be classified as bacterial, viral, or rickettsial.

Bacterial Pneumonias

Although a larger proportion of cases of milder atypical pneumonias is now recognized and the mortality from classical pneumococcal pneumonia has dropped strikingly there is still a significant mortality from bacterial pneumonia, particularly among the aged From the standpoint of management, it matters little whether the pneumonia is lobular or lobar but it is essential to determine the causative organisms Hence, for this discussion we shall employ a classification based on etiology rather than on anatomical distribution, or pathological character although one finds it rather difficult to classify the different forms of bacterial pneumonias on this basis as not infrequently more than one pathogen may be responsible for the infection Bacterial

pneumonias may be grouped into three main types. The first group comprises the so-called primary pneumonia—pneumococcal, streptococcal, staphylococcal, *H influenzal*, those due to *Klebsiellae* and tuberculous, of which the pneumococcal is the prototype Although classical pneumococcal pneumonia appears to be diminishing in frequency the pneumococcus still remains the commonest invader of the lungs However within recent years, there has been a marked increase in the number of pulmonary infections due to the *Klebsiella* group of organisms. The reason for this increased incidence of *Klebsiella* pulmonary disease may be due to improved case finding, both clinical and bacteriologic and/or as a result of disturbance of bacterial homeostasis by the widespread use of such antibiotics as penicillin with resultant superinfection by *Klebsiella* pneumoniae. In the second group are included the few bacterial pneumonias which are the result of systemic infection typhoid fever tularemia, and brucellosis There has been in recent years a striking decline in incidence of pneumonias of the first group and the third group (including as it does infections secondary to disturbances of pulmonary function produced by bronchial obstruction atelectasis aspiration, stasis and the like) has become the most numerous and most important.

Treatment of Pneumonias

Since pneumonia is no longer considered a disease entity but rather an organ response to a variety of etiological agents, we find that its treatment in general is the same for all types It includes the selection of the proper antimicrobial agent, in addition to good nursing care, rest, nutrition, and symptomatic relief The length of time that elapses between the onset of pneumonia and the beginning

of treatment is of great importance, especially in persons over the age of fifty and those with heart disease tuberculosis diabetes mellitus alcoholism or similar chronic diseases Hence one should institute therapy as soon as the clinical diagnosis has been made and the necessary material has been collected for laboratory study The physical findings of consolidation in a typical fully developed case of pneumococcal lobar pneumonia are characteristic, but seem to be infrequently encountered in recent years In many cases physical examination reveals only impaired resonance or rales without classical bronchial breathing. X ray examination is desirable in order to demonstrate the extent or density of pulmonary involvement The clinical and roentgenological findings in the pneumonias due to various bacteria are rarely sufficiently characteristic to suggest the etiological diagnosis. However the classical history (sudden onset of chills and fever pain in the side cough, and expectoration of rusty sputum) and the physical findings as described above when encountered are, of course suggestive of pneumococcal pneumonia. Furthermore a history of a severe sore throat for several days preceding the pneumonia would suggest a streptococcal affair The demonstration of multiple cavities by x ray examination should direct suspicion toward staphylococci or *Klebsiellae* as the causative agents

Pneumococcal Pneumonia

It would appear that penicillin in almost any dosage and form will give excellent results in the treatment of pneumonia due to the pneumococcus The three schedules which appear most useful are the administration of aqueous crystalline penicillin (100 000 units every eight to twelve hours) the daily injection of procaine penicillin preparations

(300 000 to 600 000 units) or oral penicillin tablets—250 000 units every three to four hours or pills containing 300 000 units of penicillin and 0 75 Gm. of benemid every six to eight hours The length of therapy is dependent upon the individual case, although in most instances treatment should be continued for five to seven days In those cases not amenable to penicillin therapy one may employ one of the other antibiotics preferably tetracycline or oxytetracycline 500 mg every six hours by mouth or erythromycin 200-400 mg every four to six hours by mouth

Streptococcal Pneumonia

Most cases of pneumonia due to the hemolytic streptococcus will respond well to penicillin therapy or in penicillin sensitive patients one of the wide-spectrum antibiotics as outlined for pneumococcal pneumonia. However the response is not as dramatic and drug treatment is of necessity given over a longer period of time (ten to fourteen days)

Staphylococcal Pneumonia

Staphylococcal pneumonia represents a serious form of pneumonia, in that it is not infrequently hematogenous in nature and may be rapidly fatal unless diagnosed and treated early Penicillin crystalline G intramuscularly 300 000 units every two to three hours is often successful, but, in view of the increasing number of penicillin resistant staphylococci it is important to employ sensitivity studies early in this illness Erythromycin 300 to 500 mg every four to six hours represents the best drug if penicillin is ineffective or cannot be used. Treatment with either antibiotic is usually required for fourteen to twenty-one days,

Hemophilus Influenza Pneumonia

Hemophilus influenza pneumonia is seen as a frequent complication of acute laryngotracheobronchitis in infants or as a primary disease in both infants and adults The prog nosis is usually good, except in the very young or in debili tated persons Since the causative organism is susceptible to the broad spectrum antibiotics good results have been obtained with tetracycline or oxytetracycline 250 to 500 mg. by mouth every four to six hours depending on the severity of the infection

Klebsiella Pneumonia

Klebsiella infections of the lungs represent the most chal lenging problem in the antimicrobial therapy of bacterial pneumonias. First of all, the diagnosis of *Klebsiella* pul monary disease is a difficult one to make in many instances The disease may be acute or chronic with often a spectrum of gradations between the acute fulminating case and the insidious chronic one. Some of the chronic cases probably were acute at one time or another and represent those who do not die in the acute episode nor resolve completely It is therefore not proper to consider the acute case as an entity different from the chronic one. *Klebsiella* pneumonia may be likened to pulmonary tuberculosis in that the infection is resistant to therapy and tends to produce necrosis and fi brosis. According to some investigators sulfadiazine 1 Gm every four hours has been effective if given early in the disease, however this experience is not uniform Certainly penicillin is of no value and there is reason to believe that it may be of some harm as far as subsequent antibiotic ther apy is concerned. Successful results have been obtained with streptomycin 1 to 2 Gm. daily intramuscularly and

members of the tetracycline group 250 to 500 mg. every four to six hours Also encouraging results in our clinic have been observed with the use of a combination of chlortetra cycline oxytetracycline and chloramphenicol (COC) Regardless of the drug therapy employed, it must be given over a relatively long period of time five to ten weeks Nevertheless it appears that *Klebsiella* pneumonia, like tuberculosis, is not amenable to complete cure with the now available antimicrobial agents that many cases will relapse and a definite proportion of cases will march to their death because of poor natural resistance for which drugs cannot compensate or because of excessive virulence of the organisms

Pneumonia Due to Mixed Infections

As the frequency of primary bacterial pneumonia dimin ishes it should be recognized that an ever increasing propor tion of pneumonias will be found to be due to mixed in fection, and in such cases it is mandatory that a search be made for underlying factors predisposing to pneumonia. In every patient who has had recurrent attacks of pneumonia, especially if the same lobe has been repeatedly involved, the likelihood of bronchial disease is strong Bronchiectasis, bronchial adenoma, bronchogenic carcinoma and atelectasis of other cause must be excluded in such cases In an aging population constant vigilance must be maintained for pul monary neoplasm which in its early stages may produce or simulate a pneumonic process. Another disease increasing in frequency as a cause of chest pain blood expectoration, and fever is pulmonary infarction In our experience, many so-called postoperative pneumonias are actually the result of embolism and a considerable proportion of pneumonias occurring under other circumstances prove to be infarction

Since most of these pulmonary infections are due to mixed organisms treatment with tetracycline or oxytetracycline 250 to 500 mg. every four to six hours seems advisable Not infrequently the response to therapy is not dramatic and it is often necessary to continue drug therapy for relatively long periods of time ten to fourteen days In postoperative cases infants alcoholics, or elderly patients with impaired reflexes in which a therapeutic response is lacking one naturally thinks of an aspirative pneumonia and appropriate procedures should be instituted

Management of Complications

A search for complications should be made in every patient with bacterial pneumonia who does not respond promptly to chemotherapy Most frequently encountered are pleural complications.

Pleural Effusions

Small asymptomatic pleural effusions are common accompaniments of pneumonia but scarcely deserve the title of complications since treatment is not required. Moderate sized or massive pleural effusions occur not infrequently In the majority of instances of bacterial pneumonia these effusions are responsible for few symptoms so long as antibiotic therapy is continued. Aspiration usually reveals a clear or only slightly cloudy fluid which is sterile on culture. Large sterile exudates of this type were not encountered prior to the development of chemotherapy and they may be properly considered a new entity best designated as the sterile postpneumonic effusion Many such effusions particularly those of moderate size will resorb without local therapy under continued systemic administration of antibiotics The larger effusions present a more serious problem.

So long as systemic antibiotic therapy is continued, the effusion remains sterile on culture and the patient remains afebrile, but after the termination of antibiotic treatment, symptoms develop and aspiration may then reveal frankly purulent fluid. In patients with persistent large sterile effusions which recur after repeated needle aspirations it may be assumed that the pleural space cannot be obliterated by expansion of the lung because the lung has become incarcerated in a fibrinous envelope Treatment under these circumstances should consist either of surgical decortication or the employment of streptococcic enzymatic debridement.

The management of frankly purulent effusions or empyema has been revolutionized during the last decade by the introduction of penicillin, streptodornase and surgical decortication. There is no longer a place for tube or open drainage in the treatment of empyema. A majority of empyemas can be successfully treated medically by daily aspiration and instillation of 50 000 units of penicillin in addition to high level systemic penicillin therapy If the aspirations are performed skillfully and regularly reexpansion of the lung can usually be secured without loculation If despite instillation of penicillin, the lung fails to reexpand because of fibrin deposits enzymatic decortication by use of streptodornase should be attempted If all efforts at medical therapy are unsuccessful, surgical intervention is required. It should be emphasized that the role of surgery is not, as in the past, to control infection by drainage. Control of infection is as a rule effected by antibiotic therapy and surgery is required only to decorticate the lung in order to permit obliteration of the pleural space

Abscess of the Lung

The need for surgical drainage of pulmonary abscesses is

equally rare at present, as systemic antibiotic therapy in high dosage will control most abscesses complicating pneumonia. Occasionally intracavitary instillation of penicillin may be attempted in large abscesses which are readily accessible to needle aspiration If these methods fail to secure closure of the abscess cavity thoracotomy and pulmonary resection may be carried out with greater safety and better preservation of pulmonary function than could have been achieved by surgical drainage A word of warning is in order however concerning the medical treatment of pulmonary abscess We have treated several patients with large pulmonary abscesses and have obtained by prolonged systemic penicillin therapy complete resolution of the inflammatory process so that the ordinary roentgenogram appeared normal. Use of planigrams and bronchograms however revealed residual cavities. This finding presumably accounts for the considerable frequency of relapse after apparent medical cure of pulmonary abscess Obviously in those cases presenting penicillin resistant organisms the choice of antibiotic is dependent on the identity of the infecting organisms and their sensitivity

Meningitis

Meningitis is now a relatively uncommon complication of pneumonia. Lumbar puncture is indicated whenever neurological signs suggest possible meningeal irritation but in most instances frank meningitis will not be found. (For treatment see chapter on Infections of Central Nervous System)

Acute Bacterial Endocarditis

Acute bacterial endocarditis complicating pneumonia can readily be controlled by adequate doses of antibiotics if the

presence of this complication is recognized before extensive valvular damage occurs (For treatment see chapter on Infections of Cardiovascular System.)

Purulent Pericarditis

Purulent pericarditis should be treated by local instillation of penicillin as well as by systemic administration in high dosage

Pneumonias usually occurring with systemic disease, tu berculosis typhoid fever tularemia, and brucellosis are dis cussed under the specific disease. (For treatment see chapter on Infections of Cardiovascular System.)

Nonbacterial Pneumonias

Primary Atypical Pneumonia

During the past few years a type of pneumonia of doubt ful etiology has received considerable attention. A variety of names have been used in designating this type of pneu monia infection and, because of the failure to isolate a com mon pathogenic bacteria, the term virus pneumonia has been widely employed. Although there is some experimental evi dence to justify this term, the etiology is by no means established and until the causative agent, or agents are deter mined the disease is best referred to as primary atypical pneumonia, etiology unknown. Such a term differentiates this type of pneumonia from those atypical pneumonias caused by known agents which produce a similar clinical syndrome such as virus influenza A and B ornithosis, psittacosis meningopneumonitis and rickettsiae.

In view of the unpredictable course of events in patients suffering with primary atypical pneumonia, any improvement following therapeutic measures may be considered incidental to the natural course of the disease Although there is no

specific therapy for this disease there have been reports suggesting that one of the tetracyclines (250 mg every four hours) had a favorable effect on the course of the disease and is worthy of trial in the more severe cases

Epidemic Influenza

Antibiotics are of no value in the treatment of an uncomplicated case of epidemic influenza and are of doubtful value in preventing certain complications of this disease but are useful in the treatment of such bacterial complications as otitis media, sinusitis and pneumonia In view of the relative frequency with which these bacterial complications occur in the extreme of life and in debilitated individuals it is common practice to employ one of the wide spectrum agents prophylactically preferably tetracycline or oxytetracycline 250 to 500 mg. orally every four to six hours in such instances as well as in the treatment of the bacterial complications

Psittacosis (Ornithosis)

The development of symptoms and signs indicative of an atypical form of pneumonia in a person who has recently had contacts with parrots parrakeets pigeons and the like should suggest the possibility of psittacosis. At present, the best therapeutic results have been obtained with chlortetracycline 250 to 500 mg. every four to six hours by mouth for at least ten days Intravenous chlortetracycline 500 mg. every twelve hours may be used in selected cases

Chronic Bronchopulmonary Infections

The treatment of chronic infections of the respiratory tract represents the outstanding challenge to the practicing physician so far as infections of the respiratory tract are concerned. In such cases as chronic bronchitis bronchiec

tasis and chronic pneumonitis it is often difficult to be sure which organisms are pathogens and which are harmless saprophytes Therefore the antimicrobial agents cannot be administered as rationally as in, for example, acute pneumococcal pneumonia and, for this reason the treatment of these chronic infections is to some extent a matter of shots in the dark

Obviously the possibility of drug resistance and toxicity and the development of new infections with resistant organisms especially staphylococcus aureus and *Klebsiella*, represent the major problems in the treatment of chronic diseases of the chest. It is probable that the damaged bronchi, except in early cases, never return to normal as a result of antimicrobial therapy but symptoms may be abated temporarily and when these recur as a result of reinfection subsequent treatment may yield similar results

Since gram positive organisms are responsible for the majority of such infections penicillin has been used most beneficially particularly during the acute flare-ups, although its use has proved disappointing over long periods of time. For this reason it is necessary to interrupt penicillin therapy and employ one of the tetracyclines erythromycin, COC or a sulfonamide in order to control the infection

Although there can be no hard and fast rules set down which one can follow in every case of chronic bronchopulmonary infection, the following are generally accepted. First, penicillin is the drug of choice for infections in which gram-positive organisms are involved. Second, oral administration of penicillin in dosages of 500 000 units every four to six hours is preferable to parenteral injections. When intramuscular penicillin is indicated, the concomitant use of an antihistaminic drug is advisable. This is also applicable in a small percentage of allergic patients who are receiving

out irritating the tissue membranes or inducing toxic re actions The comparative lack of success of these attempts can be appreciated when it is realized that until two decades ago acceptable therapeusis of genitourinary infections re volved about mandelic acid methenamine arsenicals alter ations of urinary *p*H and forced fluids with none of these being wholly satisfactory Since then, however the roster of agents with specific activity against invaders of the genito-urinary system has been vastly enlarged by the discovery first of the sulfonamides and later the antibiotics. As a consequence, the response of genitourinary infections to these newer antibacterials as seen today is understandably spectacular in comparison with the response seen before their introduction And yet, while specific genital infections have yielded almost completely to antimicrobial agents an equivalent degree of success has not been observed in infec tions of the urinary tract While the period of disability and suffering formerly associated with the latter infections has been sharply reduced it is not an uncommon experience that a significant proportion of urinary tract infections still fail to improve during antibacterial therapy or recur after variable periods of time following discontinuation of it. Obviously this situation is incapable of improvement unless the factors contributing to these therapeutic failures are known and understood

Factors Contributing to Therapeutic Failures

Many simple and almost all persistent or recurrent infections of the urinary tract are related, directly or otherwise, to its functional disorders Quite obviously antibacterial therapy of these infections is secondary to correction of the basic disorder which in turn presupposes accurate recogni tion of the fundamental cause of the dysfunction The hy

drostatic relationship of fluids in the various tissues and organs of the urinary tract may be so profoundly altered by obstructions tuberculosis, foreign bodies tumors fistulae congenital anomalies etc., as to produce abnormalities in their physiology and bacteriology In addition any obstructive pathology may in itself act directly as a focus of infection

One of the commonest predisposing causes of and obstacles to recovery from, urinary tract infections is urinary stasis It is well recognized that complete recovery from urinary tract infection is not to be expected until appropriate measures have been taken to remove all pathologic lesions or remedy any condition which interferes with free urinary drainage

Foci of infection centered in other areas of the body also have a bearing upon urinary tract infections In addition to being possible reservoirs from which infection spreads to the urinary tract, they may by reducing the patient's resistance or immunologic capacities predispose to infection of the tract

From the foregoing it is apparent that the degree of success of any antimicrobial therapy will depend primarily upon the determination of the existence and location of all lesions which interfere with free urinary flow and the recognition of foci of infection in contact with, or draining into the urinary tract.

Therapeutic failure quite frequently results from the use of inadequate dosage of the antibacterial agent. In urinary tract infections the offending organisms are not only present in the involved tissue but also in the urine Obviously removal of organisms from one site and not from the other will, at best, result only in temporary remission of the infection Quite frequently the selection of an antibacterial

agent for use in a urinary tract infection is based on the demonstration that it is excreted in the urine in high concentration and consequently can be expected to be effective This assumption is probably valid if the primary intention is to sterilize the urine It should be remembered, however that recommendations as to dosage are based on *in vitro* laboratory determinations of the urinary concentration of antibacterial agents which inhibits various test organisms Since substances excreted by the kidney are more concentrated in the urine than in the blood serum or tissue fluids the demonstration of an inhibitory urinary concentration is no guarantee of the existence of a therapeutic blood or tissue concentration. Hence, the selection of an antibacterial agent and the dosage in which it is to be used should be based not only on the attainable urinary concentration but also on the attainable tissue concentration. The existence of barriers such as round cell infiltrations, cicatrices impaired renal function or vascularization, mitigating against effective saturation of the tissue with the antibacterial agent, must also be considered.

Therapeutic failures are also attributable to resistance of the invading organisms to the antibacterial agent. Here it is important to distinguish between natural and acquired resistance. Natural resistance reflects the ability of an organism to withstand the inhibitory effects of the antibacterial agent prior to exposure to it. From a practical standpoint, the definition is referable to resistance to body fluid or tissue concentrations attainable with dosages that are unattended by serious toxic manifestations. Acquired resistance refers to the ability of an organism to withstand the inhibitory effects of an antibacterial agent, an ability which was not apparent prior to exposure to the agent but became evident following this exposure For example, gram

negative bacilli, such as *E coli* are naturally resistant to penicillin *i e.*, penicillin concentrations attainable with moderate penicillin dosages On the other hand, some strains of these same organisms prior to exposure to streptomycin in therapeutic doses succumb to its action Under appropri ate conditions however they may become very tolerant of high concentrations of this agent. These organisms are then considered to have acquired resistance. Without debating the mechanisms which have been postulated to ex plain this acquired resistance the predominating opinion is inclined to the view that when it occurs it is associated with conditions that foster poor contact between the anti bacterial agent and the organism

More recently it has been shown that organisms not only may acquire resistance to a single specific agent but also may develop cross-resistance to those antibacterials which possess similar antimicrobic activities While the actual clinical significance of this observation remains to be as sessed the possibility of its occurrence should not be ignored

Choice of Antimicrobial Agent

The selection of an appropriate agent for use in a specific case of urinary tract infection is an intricate problem The site of infection, the nature and number of infective agents the presence or absence of lesions the nature and presence of dysfunctions in organs other than the urinary tract, the sensitivity of the patient to drugs the antibacterial suscepti bility of the invading organisms are some of the considera tions which prevent the laying down of hard and fast rules Assuming that the focus and the extent and type of infectious process have been defined then the choice of antimi crobial agent depends perhaps most importantly on the

identification of the bacteria to be treated. In acute infections and under conditions where time and inadequate facilities preclude urine cultures examination of stained urinary sediments can be quite helpful in this respect. By this means it is possible to determine in many cases whether one or more organisms are involved and at the same time to obtain some clue to the morphologic and possibly the generic identity of the organisms. This information, coupled with a knowledge of the antibacterial spectra and pharmacologic behavior of the different antimicrobial agents will permit institution of therapy. This procedure constitutes the bare minimum upon which to base a rational therapy. In cases that fail to clear on such a course of treatment or in chronic or recurrent infections a complete urologic, roentgenologic and bacteriological urine study including culture and antibiotic susceptibility tests is indicated

Recent studies by us cast doubt upon the reliability of a single urine specimen for culture as a basis for determining the causative agent of a urinary tract infection. In a series of fifteen patients with urinary tract infections none of whom had had instrumentation or had received antibiotics, and from whom urine specimens were collected by regular nursing personnel, it was not possible to demonstrate the same bacteriology in two consecutive specimens taken within a twenty four hour period in eleven of the cases (seventy four per cent). It seems very unlikely that such an intrinsic urinary flora variation would exist in patients with a stable homeostasis unmodified by internal drug therapy or external urethral ...lation. While this possibility has not been enti... ...ted it would ... more likely that under these ... the ur... ...ould be expected to remain ... would most likely be ... the

time of taking the specimen It is apparent that the selection of an antibiotic with most specific activity as well as evaluation of its effectiveness depends upon unequivocal identification of the infecting flora, a goal which is attainable only as a result of the collection and examination of multiple pre therapy specimens by individuals trained in the performance of these procedures

The bacteriological examination of multiple pre-therapy urine specimens (two specimens taken within twenty four hours of each other) can be completed within thirty six to forty-eight hours to the point where presumptive identification of the offending organisms has been made and their relative antibiotic susceptibility determined. Toward this end, the following procedure has been found adequate. Immediately after collection of the initial specimen 15 ml. of urine are centrifuged at 3000 R.P M in a sterile tube The supernate is decanted aseptically One portion of the sediment is streaked on appropriate solid differential culture media A second portion is distributed uniformly with a sterile swab on the surface of a blood agar plate upon which subsequently are deposited appropriate antibiotic disks. This plate serves for determinations of antibiotic susceptibility A third portion is used to prepare smears for microscopic examination after appropriate staining. Following overnight incubation the plates are read. By this time the second consecutive specimen has been collected and is ready to be subjected to the same procedure Thus, it is possible to determine the morphology of the bacterial flora in the specimens correlate the morphologic types found in culture with those seen on smear and ascertain the antibiotic susceptibility all within a period of time not exceeding forty-eight hours

Incidence of Urinary Tract Pathogens and Their Antibiotic Susceptibility

While many gram positive and gram negative bacteria have at one time or another been implicated in urinary tract infections only a relatively small number occur repeatedly and frequently Table 7 shows the incidence with which various bacteria have been encountered in urinary tract infections seen at the Philadelphia General Hospital (Blockley Division)

It is apparent that the gram negative *bacilli* are encountered about 2½ times as frequently (seventy two per cent) as gram positive cocci (twenty-eight per cent) In this latter group enterococci also occur about four times as frequently as the other cocci. Obviously urinary tract infections are most frequently (ninety five per cent) associated with bacteriological incitants which are normally indigenous to the intestinal tract.

Our recent studies on the relative antibiotic susceptibility of pathogens most frequently associated with urinary tract infections yielded the data shown in Table 8

Considering the data in the two preceding tables, it is seen that for about seventy per cent of the pathogens associated *with urinary tract infections there are* one or more antibiotics which are effecive *in vitro* against ninety per cent or more of the strains tested. For *Escherichia* and *Klebsiella* organisms there is the combination of chlortetracycline-oxytetracycline-chloramphenicol (COC) Erythromycin and carbomycin and COC have a high specificity for enterococci and *M pyogenes var aureus* particularly those which are penicillin resistant. Despite its high degree of *in vitro* activity carbomycin has proven clinically disappointing *Str viridans* and *Str pyogenes* are uniformly susceptible

to all the agents shown *Proteus Pseudomonas* and *Para colobactrum* organisms comprising thirty per cent of uri nary pathogens may be regarded as relatively refractory to antibiotic activity although *Paracolon bacilli* are signifi cantly less so than either *Proteus* or *Pseudomonas* Either streptomycin chloramphenicol or COC appear to have activity against fifty to sixty per cent of paracolon strains studied.

Not all species of *Proteus* organisms are equally refractory to antibiotic activity Studies in our laboratories have shown that the incidence with which the different species of *Proteus* are encountered are *P mirabilis* thirty-eight per cent, *P vulgaris* thirty per cent *P rettgeri* twenty-one per cent, and *P morgani* eleven per cent Only the vulgaris and morgani strains show a significant susceptibility to anti biotics In the case of the former about sixty five per cent of strains are susceptible to COC and only twenty per cent to the other agents Approximately fifty per cent of morgani strains are susceptible to either chloramphenicol or COC while chlortetracycline and oxytetracycline are ineffective. Mirabilis and rettgeri species are relatively resistant to all antibiotics While there are reports which indicate that sulfasoxazole (gantrisin) is particularly effective against species of *Proteus* our experience has been that it possesses no significantly greater activity against these organisms than other sulfonamides such as sulfadiazine or mixtures of the sulfapyrimidines Recent work suggests that a combina tion of streptomycin and oxytetracycline are clinically ef fective against *Proteus* infections despite lack of *in vitro* activity

Recent work on the antibacterial nitrofurans has led to the introduction of nitrofurantoin N (5-nitro-2 furfuryli dene) 1 aminohydantoin (Furadantin) as an agent for the

treatment of urinary tract infections Claims for this drug include wide spectrum activity stability and relatively little tendency to permit development of bacterial resistance. It does not appear to lower the fecal bacterial count, suggesting that no overgrowth of fecal fungi is to be expected during therapy Untoward effects, such as nausea and emesis have attended its use These disappear with withdrawal of the drug Furadantin is especially interesting because of its potential effectiveness in infections due to *Proteus* organisms Studies in our laboratory have shown that seventy five per cent of 113 strains of *Proteus* are inhibited by 10 mg. per cent or less of the agent, a urinary concentration which it is claimed is apparently not difficult to attain with moderate dosages More extensive clinical trials are indicated before it will be possible to assess the practical value of this agent.

Polymyxin B has been shown to possess an unusual level of activity against strains of *Pseudomonas* but, in view of its nephrotoxicity should be used only with caution in patients with urinary tract infections caused by these organisms

Table 9 represents a guide to the selection, dosage, and duration of therapy of antibacterial agents based on susceptibility of various organisms most commonly found in urinary tract infections in which a single organism is the causative etiology

Epididymitis

Acute epididymitis may be gonococcal, tuberculous or nonspecific in origin. Where the etiology of the epididymitis is the gonococcus the treatment of choice is penicillin, 600 000 units daily for at least three days If for any reason, penicillin is contraindicated, or the response is unsatis

factory tetracycline or oxytetracycline 250 to 500 mg. every six hours for seven days may be used with anticipation of gratifying results Chronic gonococcal epididymitis while seldom seen today would be treated as the acute disease and following subsidence of the inflammatory reaction at tention should be focussed on associated lesions of the gen ital tract or urethra

In tuberculous epididymitis medical treatment consists of streptomycin 1 Gm every third day and PAS 12 Gm per day for at least six months Isoniazid, 250 mg per day may be used as adjunct therapy with streptomycin or PAS Every effort should be made by appropriate thorough urologic and general examination to ascertain the presence of tuberculous infection elsewhere in the body since epi didymitis due to the tubercle bacillus is only one manifesta tion of tuberculosis

In nonspecific epididymitis every effort should be made to isolate the causative organism, following which, therapy is based on sensitivity tests. When it is not possible to isolate the causative organism, therapy consisting of penicillin 400 000-600 000 units and streptomycin 0.5 Gm. daily should be instituted. Alternatively this protocol may be supple mented with gantrisin 1 Gm. four times daily Tetracycline or oxytetracycline are indicated 250 to 500 mg every six hours whenever penicillin streptomycin, or the sulfona mides are not.

Prostatitis

This disease most frequently has a gonococcal etiology although pyogenic organisms and the tubercle bacillus are occasionally found to be the causative agents When abscess formation follows acute prostatitis it rarely or never com plicates gonococcal infections except as the result of trauma.

More often it is the result of hematogenous or lymphatic spread of an infection whose primary site is other than the urethra although this locus can also be the site of primary infection.

The real value of antimicrobial agents in prostatitis still remains to be assessed, although penicillin, streptomycin, sulfonamides and the tetracyclines are used. Certainly these agents are efficacious in the acute gonococcal cases before secondary invaders become established. However when this occurs antibiotics produce less gratifying results because these bacteria are less susceptible to them and it becomes increasingly difficult to secure therapeutic concentrations in the poorly draining prostate

The treatment of tuberculous prostatitis should be governed by the same principles established for therapy of the pulmonary and renal forms of tuberculosis

Urethritis

Antimicrobial therapy of gonorrheal urethritis is discussed in the section on Venereal Diseases

Nonspecific urethritis due to bacterial causes may be caused by any of the organisms usually involved in urinary tract infections Where the etiology is coccal, penicillin or erythromycin in moderate dosage is indicated. Infections resistant to these agents may be successfully treated with tetracycline or oxytetracycline in dosage of 250 to 500 mg four times a day for five days Sulfonamides especially gantrisin and elkosin, may at times be useful adjuncts. For urethritis associated with prostatitis 400 000-600 000 units penicillin and 1 Gm. streptomycin per day together with gantrisin 1 Gm. four times a day for one week gives satisfactory therapeutic response.

Abacterial urethritis remains a therapeutic problem. Recently evidence has been proposed which suggests that pleuropneumonia like organisms (PPLO) whose real nature is not yet understood, may be involved in this disease. While all of the antibiotics have been tried with none producing startling results streptomycin 1 Gm per day for one week and oxytetracycline 250 mg four times a day for an equal period of time have been used with some success in some patients There are those who regard oxytetracycline as superior to streptomycin

Puerperal Sepsis

Infection within the female genital tract may occur during the puerperium or as a complication of abortion. Most cases of puerperal infection are caused by anaerobic streptococci although other organisms such as hemolytic streptococci, staphylococci, *E coli Cl tetani, Cl perfringens* and others may be responsible Mixed infections occur most often following illegal abortions If puerperal infection is suspected, a culture is taken and antibiotic therapy instituted promptly Large doses of penicillin (aqueous penicillin G 300 000 to 600 000 units intramuscularly every two to three hours) and streptomycin (0.5 Gm intramuscularly every four to six hours) are administered initially with modification of therapy if necessary In resistant infections or in patients sensitive to penicillin tetracycline or oxytetracycline (500 mg. every four to six hours orally or intravenously every eight to twelve hours) may be administered. Many investigators prefer the latter drugs as the initial form of therapy

TABLE 7

INCIDENCE OF BACTERIA IN URINARY TRACT INFECTIONS
(804 Strains)

Organism	*Per cent Incidence*
Escherichia sp	33 1
Enterococci	22.5
Proteus sp	17 4
Paracolobactrum sp	8.2
Klebsiella sp	7 7
Ps aeruginosa	5 6
M pyogenes var aureus	3 9
Str viridans	1 3
Str pyogenes	0.3

TABLE 8

RELATIVE ANTIBIOTIC SUSCEPTIBILITY OF URINARY PATHOGENS
PER CENT OF STRAINS CLASSIFIED AS SUSCEPTIBLE TO

Organism	*S*	*P*	*CT*	*O*	*C*	*COC*	*E*	*CM*
Escherichia sp	61	—	33	48	83	94	—	—
Proteus sp	23	—	3	9	32	34	—	—
Paracolobactrum sp	49	—	20	29	64	61	—	—
Klebsiella sp	43	—	40	51	65	92	—	—
Ps aeruginosa	10	—	4	18	6	11	—	—
Enterococci	—	51	70	68	80	88	90	90
M pyogenes var aureus	—	50	85	81	87	95	99	99
Str viridans	—	99	100	100	100	100	99	99
Str pyogenes	—	100	100	100	100	100	—	—

S = streptomycin, P = penicillin, C = chloramphenicol, CT = chlortetracycline, O = oxytetracycline, COC = combination of chlortetracycline-oxytetracycline-chloramphenicol, E = erythromycin CM = carbomycin.

TABLE 9

Guide to Selection, Dosage, and Duration of Therapy of Antibacterial Agents in Urinary Tract Infections

	Mandelamine	Gantrisin	Sulf Comb	Streptomycin	Penicill	Chlortetracycline	Oxytetracycline	Chloramphenicol	COC†	Erythromycin	Sulfadiazine	Furadantin
Minimum Daily Dosage	8 Gm	6 Gm	4 Gm	1 Gm.	600 000 units	2 Gm.	2 Gm	2 Gm.	2 Gm.	1 5 to 2 Gm.	4 Gm.	500 mg
Duration of ℞ (days)	10	10	10	5	5	7	7	7	5	5	10	7
Escherichia sp	3	1	1	2	0	1	1	1	1	0	1	1
Enterococci	3	3	3	3	2	2	2	2	1	1	3	3
Proteus sp	3	2	3	2	0	3	2	2	2	0	3	1
Paracolobactrum sp	3	2	2	2	0	3	3	1	1	0		1
Klebsiella sp	3	2		2	0	3	2	1	1	0	2	1
Ps. aeruginosa	3	2	2	2	0	3	2	3		0	2	2
M. pyogenes var. aureus	3	3	3	3	2	2	2	2	1	1	2	2
Str. viridans	3	2	2	3	1	1	1	1	1	1	2	2
Str. pyogenes	3	2	2	3	1	1	1	1	1	1	2	2

†Combination of chlortetracycline, oxytetracycline and chloramphenicol.

Polymyxin B is effective in infections caused by these organisms but is not generally used because of its toxicity

0 = No significant activity in vitro.

1 = In vitro and in vivo activity- drug of choice.

2 = Active on some strains, not on others.

3 = Significantly diminished activity in comparison with other agents.

Please note that all data under Oxytetracycline also apply to Tetracycline.

7

Antimicrobial Therapy of Specific Infectious Diseases (Continued)

INFECTIONS OF CENTRAL NERVOUS SYSTEM

Bacterial Infections

Fortunately antimicrobial agents are now available to control successfully most bacterial infections of the central nervous system. Whether the infection is diffuse as in meningitis, or is a localized abscess of the brain, the principles of therapy are essentially the same For the most part, the final outcome is influenced by such factors as the causative agent, age of the patient, duration of the illness and whether the infection is primary or secondary to skull or spinal injury mastoid or paranasal sinus disease or to sepsis elsewhere such as pneumonia, or furunculosis

Meningitis

The possibility of meningitis must be entertained in all acutely ill patients especially in those with severe and persistent headaches repeated vomiting lethargy and/or stiffness of the neck. Although the history and clinical findings are usually highly suggestive of some involvement of the meninges the final diagnosis of meningitis depends on examination of the cerebrospinal fluid. Not only will this procedure confirm the diagnosis of a suppurative type of

meningitis but it will very frequently also determine the etiologic agent, and in turn serve as a guide for specific therapy The frequency with which the various etiologic types of pyogenic infection of the meninges are encountered is roughly as follows Meningococcic—forty per cent, pneumococcic—fifteen per cent, hemolytic streptococcic ten per cent, influenzal—five per cent, staphylococcic—one per cent, miscellaneous *Klebsiella* bacilli, *Pseudomonas* gonococcic, *Salmonella* group colon bacilli, etc —four per cent. The remaining twenty five per cent include nonpurulent types especially tuberculous viral and luetic In addition, it is to be remembered that occasionally the infection is a mixed one and also in a disease such as meningitis it is important to consider the possibility of the development of a superinfection during the course of antimicrobial therapy

In general, the best results in bacterial meningitis have been obtained with penicillin against the gram-positive and *Neisseria* organisms and one of the tetracyclines chloramphenicol, polymyxin B bacitracin, or streptomycin for the gram negative bacilli. The sulfonamides still play an important role as adjuvants if nothing more than to prevent or diminish the incidence of superinfections or drug resistant organisms Although a lumbar puncture is necessary for diagnostic purposes is repeated in some cases to determine the effect of therapy and is occasionally indicated to relieve increased intracranial pressure, the fact remains that frequent lumbar punctures should be avoided. Furthermore, intrathecal therapy should be reduced to a minimum and only in selected cases does this route of administration seem necessary In view of the fact that many cases of bacterial meningitis are secondary to infections of the middle ear mastoids paranasal sinuses skin lungs etc. an intensive search for a possible focus in these areas is imperative

Every patient should be examined by a competent otolaryngologist and complete x ray studies especially of the paranasal sinuses mastoids and lungs should be performed. The urgency of this step is based on the likelihood that drug therapy will not influence a primary suppurative process and that constant refeeding of blood stream and meninges from such a focus will militate against recovery Marked clinical improvement and sterilization of the cerebrospinal fluid and blood stream do not relieve the physician of the necessity for continuing the search for possible foci since the meningitis may become reestablished if distributing foci, untouched by drug therapy remain The slightest evidence of undrained abscesses especially in mastoids or paranasal sinuses demands surgical intervention even though such findings would not call for surgery in the absence of meningitis

Meningococcic Meningitis

Meningococcic meningitis is usually a primary disease and the majority of cases respond dramatically to treatment with sulfadiazine and/or penicillin Considering the seriousness of this disease, it seems advisable to employ both antimicrobial agents routinely except in mild cases the initial dose of sulfonamide being administered intravenously sodium sulfadiazine 3 to 4 Gm as a 0.5 per cent solution followed by 1 Gm. by mouth every four hours In comatose patients the drug may be administered by a stomach tube Penicillin is given intramuscularly 1 000 000 units (aqueous crystalline penicillin) every two to three hours Very occasionally a fulminating form of meningococcic meningitis the Waterhouse-Friderichsen syndrome, with associated adrenal failure will occur and prove fatal unless the condition is readily recognized and vigorous treatment begun

promptly In addition to antimicrobial therapy the patient should be supported as though he were in crisis in Addison s disease namely—hydrocortisone (free) 4 cc. of a 25 mg./cc. solution in 1000 cc. of saline solution intravenously plus 25 mg to 50 mg intramuscularly every six hours and neo-synephrine 0 3 to 0 5 mg every one to three hours subcu taneously if systolic blood pressure falls below 80 mm. Hg

The total duration of antimicrobial therapy varies in each case of meningitis but, in general, treatment should continue for at least seven days after the patient appears clinically well. Following recovery from meningococcic meningitis one should obtain three nasopharyngeal cultures and, if positive, the patient should be given a second course of sulfadiazine, 1 Gm. by mouth every six hours for four days

Pneumococcic Meningitis

Despite the uniform susceptibility of the pneumococcus to penicillin, pneumococcic meningitis is still a very serious form of meningitis in that the infection is usually secondary to some focus elsewhere in the body Best results are obtained with massive penicillin dosage (1 000 000 units of aqueous crystalline penicillin intramuscularly every two hours) plus sulfadiazine as outlined for cases of meningococcic meningitis Because of the poor prognosis associated with pneumococcic meningitis many experienced investi gators still employ intrathecal penicillin in such cases, on the basis that the benefit derived far outweighs the danger of neurological complications resulting from intrathecal therapy Certainly in seriously ill cases a single initial intrathecal administration of penicillin (no more than 20 000 units) would seem advisable until sufficient data are avail able which demonstrate equal therapeutic results with intensive intramuscular penicillin therapy alone Since most

cases of pneumococcic meningitis are secondary to infections elsewhere in the body especially the middle ear mastoid and paranasal sinuses it is imperative that a thorough search be made for a possible focus

Streptococcic Meningitis

The treatment of streptococcic meningitis is the same as for pneumococcic meningitis Fortunately the prognosis is much better for beta streptococcic infections of the meninges than the latter in that the disease is often primary in origin and the thorny problem of eradicating foci is thus minimized

Staphylococcic Meningitis

In general, the treatment of staphylococcic meningitis is the same as for pneumococcic and beta streptococcic meningitis However the prognosis is poor in that the disease is seldom primary in nature and the causative agent is frequently resistant to penicillin. It is most important therefore to determine the sensitivity of the particular staphylococcal strain to the various antimicrobial agents Erythromycin 500 mg. every four to six hours orally or 250 mg. every six to eight intravenously has proven an effective agent in these penicillin resistant cases although equally good results have been obtained with bacitracin 50 000 units intramuscularly every six hours or one of the tetracycline group of drugs 500 mg. every four hours by mouth or 100-500 mg every six to twelve hours intravenously

Influenzal Meningitis

For practical purposes influenzal meningitis represents two diseases so far as prognosis is concerned In young infants and in the aged, particularly the disease frequently

represents an extension from an infection of the sinuses or mastoids whereas in children and young adults the disease is more often primary in nature Excellent results have been obtained, especially in young adults with the tetracycline group of drugs especially chlortetracycline orally or intra venously (2 to 3 Gm per day in divided doses every 4 hours) Sulfadiazine 4 to 6 Gm daily and streptomycin 2 to 4 Gm. daily in combination, chloramphenicol, 3 to 4 Gm daily and erythromycin 2 to 4 Gm. daily have also been used successfully

Meningitis Caused by Other Gram negative Organisms

Meningeal infections with species of *Escherichia, Pseudomonas Klebsiella* and *Proteus* are occasionally encountered and for the most part represent serious problems In general, they tend to occur in the extremes of life frequently represent complications elsewhere in the body and often are resistant to antimicrobial therapy In this group carefully performed sensitivity studies are indicated. Although some will respond to sulfonamides streptomycin, one of the tetracycline group or chloramphenicol, the results as a whole are disappointing Polymyxin B intramuscularly (30 mg every four to six hours) and intrathecally (5 mg. dis solved in 10 cc of isotonic saline solution daily for three days and then 5 mg daily on alternate days) has proved effective in many such cases and, despite its potential renal hazards its use is justified in these instances

Complications of Bacterial Meningitis

Complications and sequellae of bacterial meningitis have been reduced markedly since the advent of modern anti microbial therapy However effusion of fluid into the subdural space may occur especially in young children whereas

brain abscesses are not uncommon in patients with pneumococcic or staphylococcic meningitis The appearance of focal neurological signs vomiting coma, or the clinical impression that the course is not satisfactory should call for neurosurgical consultations

Tuberculous Meningitis and *Acute Syphilitic meningitis* will be found under their respective primary disease

Viral Infections

At this time there is no specific treatment for infections of the brain and meninges caused by viruses The antimicrobial agents have limited usefulness for the prevention or treatment of complications which may occur particularly in severe cases especially in the respiratory and urinary tracts Procaine penicillin 300 000 to 600 000 units daily or tetracycline or oxytetracycline 500 mg. every four to six hours may be tried

GASTROINTESTINAL INFECTIONS

Penicillin

Clinically penicillin is of value in peritonitis caused by the pneumococcus or streptococcus, after perforation of a peptic ulcer or rupture of the appendix. While reportedly useful in Weil's disease (leptospiral jaundice) when administered early penicillin is without beneficial effect when used alone in moderate doses in bacillary dysentery typhoid fever and gastroenteritis due to *Salmonella* and certain serotypes of *E. coli.* On occasion penicillin has produced favorable results in ulcerative colitis despite the fact that the recognizable fecal flora is not altered significantly In general however this agent has not given consistently good results in this disease It has been found useful as an aid in controlling secondary infections complicating ulcerative colitis

Penicillin alone has no effect on the growth of *Endamoeba histolytica* The sulfonamides or streptomycin have been found to be useful adjuncts to penicillin in the treatment of peritonitis, amebic dysentery amebic abscess of the liver and acute pancreatitis. When given intravenously penicillin is excreted in high concentrations in the bile and for this reason has been used by some as an agent in the treatment of infections of the biliary tract. In isolated cases, bacterial strains resistant to penicillin, notably staphylococci, are reputed to emerge after prolonged or repeated treatment, giving rise to the clinically recognized staphylococcal enteritis

Streptomycin

Clinically streptomycin has been found of value in *Shigella* infections especially when dealing with organisms resistant to sulfonamides Results in typhoid fever and other *Salmonella* infections have been variable and disappointing. In isolated cases the agent has been effective in bacteremia due to *Escherichia coli Salmonella cholerae suis,* or *Pseudomonas aeruginosa* and gastroenteritis in which *Proteus* organisms are reported to have been the predominant organism. The agent is ineffective in amebic dysentery and amebic hepatitis There are reports that streptomycin produces striking responses in cases of acute ulcerative colitis although it has not been consistently effective in the treatment of the chronic form of this disease As regards gastrointestinal tuberculosis streptomycin is the drug of choice in the management of this infection when it occurs in the small and large intestines as well as in the anorectal region. In these diseases the antibiotic is usually administered either parenterally in doses of 1 to 2 Gm. daily concomitantly with PAS Following prolonged streptomycin treat

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ment, healing of tuberculous perianal sinuses or fistulae may take place, thereby eliminating the need of surgical intervention Gastrointestinal tuberculosis in association with the pulmonary form of the disease determines the duration of improvement, frequency of relapse and ultimate recovery from the pulmonary tuberculosis. Streptomycin in combination with penicillin has been found to be a useful adjunct to surgical treatment in occasional instances of acute cholecystitis cholangitis and liver abscesses in which the causative etiology is gram-negative bacilli

Shortly after its introduction into medical practice streptomycin enjoyed great acceptance in the preoperative and postoperative management of patients undergoing surgical procedures on the bowel It has been observed that the suppressive effect of this agent, chiefly by inhibition of *E coli* streptococci, and the anaerobes occurred rapidly but subsequently it was shown that this suppression of the intestinal flora was a relatively brief one It is no longer held that streptomycin sterilizes the intestines Streptomycin in combination with penicillin has materially decreased the mortality from peritonitis caused by inflammatory and perforative lesions of the gastrointestinal tract particularly infections with a single gram negative organism or a mixed gram negative bacillary flora In the use of streptomycin for this purpose it is well to bear in mind that organisms exposed to the agent develop resistance to it rather rapidly

Chlortetracycline

Chlortetracycline despite its *in vitro* activity against the typhoid bacillus has been shown to be clinically ineffective

Most proctologists are of the opinion that only a small percentage of anorectal fistulae is tuberculous.

in this disease. Additionally the antibiotic does not effect the carrier state of either typhoid fever or that of other salmonelloses and with few exceptions has no effect on *Shigella* infections Beneficial effects due to chlortetracycline have been described in acute and chronic intestinal amebiasis It is now generally recognized that if any effect is produced, it is confined essentially to the acute rather than to the chronic form of the disease At the present time there is some question whether chlortetracycline actually possesses amebicidal action and it is for this reason that most workers recommended the concurrent administration of standard amebicidal drugs In amebic infection of the liver the antibiotic is of little value In ulcerative colitis especially during the acute stage encouraging results with chlortetracycline have been reported There is considerable doubt, however whether chlortetracycline is helpful in chronic ulcerative colitis in view of the fact that recurrence and intensification of symptoms following the administration of the antibiotic has been noted frequently A similar experience has been observed in regional enteritis While chlortetracycline apparently facilitates healing of the inflammation associated with lymphogranuloma venereum cases in which there is rectal stricture appear to be unaffected.

Like streptomycin, chlortetracycline also has a profound effect on the fecal bacterial flora This effect is temporary and mav result in the overgrowth of such organisms as *Proteus Pseudomonas Streptococcus fecalis* and *Candida albicans* When used in the preoperative and postoperative care of patients undergoing abdominal surgery the admin istration of chlortetracycline usually is accompanied by diminution in the excretion of urobilinogen in feces and urine and diminution of the excretion of bile which at times approaches a level associated with that frequently seen in

complete biliary obstruction This should be borne in mind when one is attempting to assess hepatic function at a time when chlortetracycline is being administered

Chlortetracycline administered in moderate amounts orally apparently does not impair hepatic function However in creased quantities of fat have been observed in the liver as a result of biopsy examination There is evidence to indi cate that excessive amounts of chlortetracycline cause liver injury particularly when the route of administration is intravenous Chlortetracycline is excreted by the normal liver into the bowel in comparatively high concentrations how ever in the presence of poor hepatic function and obstruction of the cystic duct, excretion is diminished. Thus the anti biotic may be useful if there is no interference with the flow of bile, particularly in infections of the biliary tract and in the prevention of cholangitis and hepatitis. Where *E coli* has been the infecting organism, chlortetracycline has been found to be effective in patients suffering with acute cholecystitis cholangioma, and biliary fistulae

Oxytetracycline—Tetracycline

In general, the antibacterial spectrum of oxytetracycline and tetracycline resembles that of chlortetracycline and chlor amphenicol. Favorable results have been reported attending its use in the treatment of patients with bacillary dysentery septicemia due to *Salmonella cholerae suis* and a few other types of *Salmonella* infections not responsive to chlor amphenicol However the agent does not appear to be of value in typhoid fever ulcerative colitis and regional ente ritis although occasionally some secondary benefits may be observed. The agent appears to be ineffective in *Proteus* and *Pseudomonas* infections despite the fact that the incidence of strains of the latter sensitive *in vitro* to oxytetracycline is

greater than to all other antimicrobial drugs polymyxin B excluded

Oxytetracycline is active against *E histolytica in vitro* and its clinical status in the treatment of this protozoal infestation is discussed under amebiasis Additionally oxytetracycline also appears to be helpful in the treatment of pinworm and *Ascaris* infestation Like the other tetracyclines oxytetracycline is excreted in high concentrations in the bile and reports indicate it to be the drug of choice in the treatment of acute or chronic cholangitis There is also evidence to indicate that oxytetracycline produces gratifying results in patients with acute cholecystitis or hepatitis although such reports are based on observations of large series of cases

Chloramphenicol

Undoubtedly the antibiotic of choice in the treatment of typhoid fever is chloramphenicol and detailed discussion of its use in this disease as well as in salmonellosis in general is given elsewhere In *Shigella* infections particularly those due to *Shigella sonnei* and *Shigella flexneri* chloramphenicol has been found to be effective particularly when these organisms are resistant to sulfadiazine While the drug is amebicidal *in vitro* clinically the results in this connection have been disappointing. Like chlortetracycline and oxytetracycline chloramphenicol is ineffective against *Giardia lamblia* the whipworm, and hookworm Like chlortetracycline, it is apparently of value in the treatment of proctitis caused by lymphogranuloma venereum Chloramphenicol appears to be ineffective in cases of acute viral hepatitis. Unlike chlortetracycline it does not appear to be excreted in the bile in a biologically active form.

Neomycin

Because of the toxicity renal and neural associated with the parenteral administration of neomycin the clinical acceptance of this drug has until recently been rather limited. However experience has now shown that much of this toxicity does not appear when the agent is administered orally although there have been isolated cases of serious toxicity to this agent when given by mouth. For this reason, neomycin is currently receiving greater attention as an agent useful in the preoperative preparation of the bowel In addition the drug appears to have value in the treatment of *Shigella* and *Salmonella* infections amebiasis peritonitis and appendiceal abscess

Preoperative Use of Antibiotics

According to Poth, the ideal intestinal antiseptic should have the following properties (1) Broad antibacterial spectrum (2) low toxicity for the host, (3) clinical stability in the presence of digestive enzymes (4) capacity to prevent the development or overgrowth of resistant bacterial variants or opportunists (5) rapidity of action (6) limited absorption from the gastrointestinal tract (7) activity in the presence of food and other foreign substances thereby allowing adequate intake of food and fluid (8) capacity to aid the mechanical functions of the bowel without causing dehydration (9) inability to irritate the gastrointestinal mucosae (10) noninterference with tissue growth and repair (11) active in low dosage (12) solubility in water (13) palatability (14) inhibitive action of excessive growth of fungi and (15) restrictive use that is to say use only as an intestinal antiseptic. There are today no agents, either singly or in combination which fulfill all of the above criteria and it is debatable

whether any of the antibiotic agents or their combinations even approach the attainment of this ideal goal.

Shortly after the synthesis of the poorly absorbed sulfonamides it became apparent that these compounds if effective would materially assist in cutting down on the difficulties of intestinal infection which usually confront the surgeon following bowel surgery However experience in this direction with these compounds revealed that they had a relatively mild antimicrobial spectrum that they had little effect upon the gram positive intestinal organisms and acted primarily as bacteriostatic agents against the gram negative bacteria. It was not until the synthesis of sulfasuxidine was accomplished that it was at all practical to alter significantly the gram negative flora of the bowel consistently Many insoluble sulfonamides have been investigated, but only three were found to have some practical value These are succinylsulfathiazole, phthalylsulfathiazole or sulfathaladine, and phthalylsulfacetamide or thalamide Of these, only succinylsulfathiazole appeared to show some promise because it not only altered the gram negative flora of the gastrointestinal tract but also aided evacuative preparation of the bowel. However following clinical use it was found that all of these substances had definite disadvantages As stated before they have narrow spectrums and are essentially bacteriostatic. Consequently they merely inhibit the multiplication of organisms Thus the use of mechanical cleansing of the bowel could not be dispensed with and in view of the considerable length of time required for this procedure the results were inconsistent and unsatisfactory unless the procedure was extended for a period of at least seven days. With the introduction of the antibiotics all have had a trial in this area. Streptomycin was the first to be tried and was immediately found unsatisfactory because of a tendency to

induce resistance in organisms When chlortetracycline became available, it was used for a similar purpose and it was observed that although this agent would markedly alter bacterial intestinal flora its use was not unattended by the occurrence of secondary pathogens such as *Staphylococcus aureus* Subsequent extensive studies have led to the con clusion that chlortetracycline in comparison with the other available intestinal antiseptics possesses no particular ad vantages Oxytetracycline has also been proposed as an intes tinal antiseptic with wide spectrum activity However so far as is known it possesses the same disadvantages as are inherent in chlortetracycline. With continued use of this antibiotic, the overgrowth of bacterial opportunists becomes apparent.

The following represents a summation of the properties and characteristics of those agents which at one time or another have been proposed as preoperative intestinal anti septics

(1) Sulfaguanadine Its activity is quite limited and slow it is inhibited in the presence of ulcerative lesions and it is absorbed in appreciable quantities Because it has been observed that sulfaguanadine when used as an intestinal anti septic produced untoward reactions which were character istic of the actions in general due to sulfonamides it is no longer used or recommended as an intestinal antiseptic.

(2) Succinylsulfathiazole It is not readily absorbed from the gastrointestinal tract and consistently inhibits the growth of gram-negative organisms without evidence of developing resistance Untoward reactions characteristic of the sulfona mides do occur although their incidence is lower approxi mately one per cent of patients It is primarily a bacteriostatic agent and hence must be administered for approximately seven days before its full effectiveness is obtained. It tends

to soften stools thereby aiding the mechanical preparation of the gastrointestinal tract. Of the various bacteriostatic sulfonamides succinylsulfathiazole is the most satisfactory *as an intestinal antiseptic*

(3) Phthalylsulfathiazole This agent possesses about the same spectrum of activity as succinylsulfathiazole although on a gram for gram basis it is twice as active as succinyl sulfathiazole It has the undesirable property of causing *stools to have a tenacious consistency* which makes the mechanical evacuation and cleansing of the bowel somewhat difficult.

(4) Phthalylsulfacetamide This agent has much the same properties as succinylsulfathiazole and phthalylsulfathiazole *It is, however absorbed to a much greater degree than the* previously named sulfonamides As a result, it is not sur prising to find that this drug shows a higher incidence of toxic reactions

(5) Streptomycin While acting rapidly streptomycin *removes almost all organisms* twenty four to forty-eight hours after oral administration, nevertheless this is followed by the rapid development of resistant strains within three to four days When given orally this antibiotic is sparingly absorbed from the gastrointestinal tract. With oral admin istration there is no toxicity As a general intestinal anti septic, it cannot be recommended because of its capacity to induce resistance

(6) Chlortetracycline A broad spectrum antibiotic with essentially bacteriostatic properties removes bacteria from the gastrointestinal tract rapidly but usually is accompanied by a luxuriant growth of resistant organisms Following the third or fourth day of suppression of the coliform organisms there is usually *an overgrowth of staphylococci* and *Proteus* organisms. The antibiotic suffers from the serious disad

vantage of being absorbed rather rapidly from the gastrointestinal tract and is not retained in appreciable amounts in the gastrointestinal tract postoperatively It is not recommended as an intestinal antiseptic.

(7) Oxytetracycline and tetracycline For the same reasons as indicated for chlortetracycline, these agents are also not recommended as an intestinal antiseptic.

(8) Chloramphenicol Because of its toxicity and relatively high absorption from the gastrointestinal tract, chloramphenicol is not recommended as an intestinal antiseptic

(9) Neomycin This is a broad spectrum antibiotic with bactericidal properties It is extremely rapid in its activity and has the capacity to sterilize the gastrointestinal tract in two to three hours when administered with castor oil However this antibiotic has only limited activity against *Shigella* organisms and shows a tendency for overgrowth of *Aerobacter aerogenes* For this reason, it is not recommended as an intestinal antiseptic when used alone. However in combination with phthalylsulfathiazole, one can expect excellent sterilization of the gastrointestinal tract, for the simple reason that the phthalylsulfathiazole inhibits the outgrowth of the *Aerobacter aerogenes* According to Poth, this combination is probably the best available material for intestinal antisepsis that we have at present. Both of these substances are absorbed from the gastrointestinal tract only to a limited degree

Diverticulitis

The role of antibiotics in the therapy of diverticulitis of the colon is that of a useful adjunct to surgical procedures which are remedial, particularly when obstruction occurs. Sulfasuxidine, 2 Gm. every six hours penicillin 1 000 000 units daily and streptomycin 1 to 2 Gm per day are all

helpful. Neomycin chloramphenicol, and the tetracyclines 250 mg. every six hours may also be indicated on various occasions

Diverticulitis of the cecum indistinguishable clinically from appendicitis requires surgical intervention, under which condition the usual antibiotics indicated in bowel operations may be used

Infantile Diarrhea

At the present time no single etiologic agent has been unequivocally incriminated as the cause of infectious diarrhea of the newborn. Numerous reports exist which attribute outbreaks of the disease to such organisms as *Ps aeruginosa, Proteus species Str fecalis Klebsiella*, and *Coliforms* Viruses have likewise been suggested. Within recent years, certain serotypes of *E coli* notably types O 111 and O 55 have been isolated by various investigators on an international scale as the predominant organism in these diarrheal outbreaks Suspect also are serotypes O 86 and O 127 the latter being a newly discovered type and isolated during a recent outbreak in the Pediatrics Department of the Philadelphia General Hospital (Blockley Division)

Of the various antibotics used, tetracycline oxytetracycline and chloramphenicol in doses of 75 mg per pound (34 mg. per kg) per day and sulfadiazine in doses of 125 mg per pound (57 mg per kg) per day are effective in controlling the diarrhea. However most favorable progress was seen in patients who received the sulfonamide. Without minimizing the role of specific therapy perhaps a more important factor in controlling diarrhea of the newborn is the maintenance of effective supportive therapy specifically designed to overcome the severe dehydration seen in these patients

Food Poisoning

The organisms which are most frequently regarded as the cause of outbreaks of food poisoning are *Staphylococci* *Salmonella* *Streptococci* *Escherichia coli* *Paracolon* *Shigella* *Klebsiella Aerobacter* group *Clostridium perfringens* and *Botulinum* The role of *Salmonella* in gastroenteritis is discussed in the section on Salmonellosis and the significance of *Shigella* has been treated in the section on Bacillary Dysentery The role of *Botulinum* is treated in Chapter 9 under *Clostridial* infections *Escherichia coli* has been discussed in the section on Diarrhea of the Newborn The exact significance of *Klebsiella Aerobacter* organisms still remains debatable. However there is no longer any question that staphylococci are involved in gastroenteritis and the present discussion will be limited to this organism

Staphylococcal Enterotoxin Gastroenteritis

The symptoms of staphylococcal enterotoxin gastroenteritis are characteristic and uniform. Since the toxin is preformed in the food which is ingested prior to the onset of symptoms the latter appear within a comparatively short time following ingestion, usually within a period of one to four hours The attack begins with diarrhea and vomiting, vomiting being the more conspicuous Weakness may be prominent and other symptoms may present themselves as for example nausea, headache, abdominal pain leg pain, or numbness of the extremities and extreme thirst. Fever may or may not be present. Not infrequently the skin is cold and clammy respiration is shallow and pulse rapid with a blood pressure of 60 systolic and 20 diastolic. The illness lasts from one-half to three days with a median of about 1½ days. Recovery is usually prompt, ranging from one to five days but in more severe cases may be prolonged to a week or

two Mortality is low, although there are authentic cases on record to show that death may occur

It is now fairly well established that not all staphylococci are capable of elaborating the enterotoxin which is respon sible for gastroenteritis Not until the kitten test was devel oped was the existence of enterotoxin demonstrable. More recently however it has become established that the entero-toxin producing staphylococci are most generally coagulase-positive strains Furthermore differentiation of serotypes among staphylococci by means of phage typing has indicated that certain of these are more frequently associated with the disease than are other types Notably one can mention types 6/47 and 42D In interpreting the results of bacterio-logical examinations of stools of patients suspected of suf fering from staphylococcal gastroenteritis it is well to remember that approximately one-third of all normal stool specimens sent to the laboratory will be found to contain coagulase-positive staphylococci which are probably in gested without ill effects through contact with a nasal car rier or in the daily food. The mere contamination of the food or the finding of staphylococci in the stools is not sufficient evidence to incriminate the food as being poten tially poisonous

Regarding the enterotoxin which is responsible for the gastroenteritis not too much is known It has never been isolated or prepared in pure form largely because satisfac tory laboratory animals which would be suitable for per forming titrations have not yet been found. Apparently the toxin is thermolabile and can be inactivated on exposure to heat at a temperature of 65 C for thirty minutes However boiling for ten minutes apparently has little inactivating effect.

There is no specific drug or serum therapy for the treat

ment of staphylococcal gastroenteritis. Essentially the treatment is symptomatic, although the possibility of utilizing erythromycin in more severe cases should not be overlooked. Dehydration is treated by the administration of five per cent solution of dextrose or physiological saline solution intravenously If the patient can take food without becoming unduly nauseated, pectin in doses of 3 Gm. four times a day or succinylsulfathiazole, 250 mg. in six doses four hours apart have been found satisfactory

Staphylococcus Enteritis Following Antibiotic Therapy

Enteritis developing during, or immediately following, antimicrobic therapy and associated with stools which reveal a predominance of coagulase-positive staphylococci has been reported Whether the micrococci found in these cases are enterotoxigenic has to our knowledge not been determined. Under the circumstances, their significance as primary incitants of the enteritis is only inferred. There are reports to indicate that erythromycin is effective in such cases

Enteritis Associated with Streptococci

Food poisoning, clinically and epidemiologically indistinguishable from staphylococcal gastroenteritis appears with increasing frequency Enormous numbers of alpha hemolytic streptococci, specifically *Streptococcus fecalis* have been found in food from which neither staphylococci or other recognized intestinal pathogens could be cultivated. In outbreaks of this type and whenever the incubation time is between two to eighteen hours and the laboratory finds several million organisms, mostly *Strep fecalis* per gram of the suspected food it is probably justified to regard the gastro-

enteritis which is observed as streptococcal in nature How ever in the light of the fact that the food poisoning poten tialities of various bacteria have been judged by the quanti tative rather than the qualitative predominance and that the identification of the streptococci in most laboratories is to be regarded as unsatisfactory the real significance of this organism as an etiologic agent in food poisoning is debatable So far as is known, gastroenteritis due to *Streptococcus fecalis* has never been fatal, and, like the enteritis due to staphylococci, it is not controllable with any specific the-rapy Treatment is usually supportive again bearing in mind the specific activity of erythromycin. Particular attention should be paid to the need for overcoming the dehydration associated with this disease.

SALMONELLOSIS

The genus *Salmonella* comprises gram negative non sporing motile bacilli which are pathogenic for man, animals, or both. Species within the genus are closely related and classification into serotypes of which about 200 are known is based upon antigenic analysis of the somatic (O) flagel lar (H) and Vi components

Salmonella fall into three groups as regards distribution and relationship to human disease (1) Primary human pathogens including *S typhosa* *S paratyphi* (paratyphoid A) *S schottmuelleri* (paratyphoid B) and *S hirschfeldii* (paratyphoid C) Of these *S typhosa* is of most importance in this country *S schottmuelleri* is the commonest, *S para typhi* and *S hirschfeldii* occur only rarely in the United States

(2) Primarily pathogens for animals and birds but also cause disease in man. In this group are found the majority

of *Salmonella* and while their incidence varies with geographical location the following represent those most frequently encountered in humans in the United States *S typhimurium S cholerae suis S oranienburg S montevideo S newport S enteritidis S panama* and *S anatis*

A study of *Salmonella* infections excluding typhoid fever at the Philadelphia General Hospital (Blockley Division) during the years 1949-1953 revealed a total of ninety-three cases in adults and children with the incidence shown in Table 10

(3) Primarily pathogenic for animals or birds only this group is rapidly becoming smaller as additional members are reported to be the cause of disease in man.

There are three main types of clinical manifestations of salmonellosis in man, (a) enteric fever (b) gastroenteritis and (c) localizing with foci in one or more organs, usually accompanied by septicemia. While any of the *Salmonella* is capable of producing one or all of these clinical manifestations, those involved most frequently in enteric fevers in this country are *S typhosa* and *S schottmuelleri* Conspicuous by the frequency with which they are isolated in gastroenteritis is *S typhimurium* and *S enteritidis* *S cholerae suis* on the other hand, is more frequently associated with septicemia and infections tending to manifest localization.

Many *Salmonella* are capable of establishing themselves in the host's tissues to produce a more or less permanent carrier state In this connection, *S typhosa* is notable the carrier state occurring in about three per cent of convalescent cases Among healthy carriers *i e* contacts with *Salmonella* but without prior history of disease various *Salmonella* including *S typhimurium S montevideo S newport* etc have been found

In discussing antimicrobic therapy of salmonellosis it is necessary to separate typhoid fever from infections caused by other *Salmonella* strains Generalizations are not feasible because our knowledge of the efficacy of antibiotics on the clinical and bacteriological course of typhoid fever is greater and more succinct than that which we possess as regards treatment of other *Salmonella* infections

Antimicrobic Therapy of Typhoid Fever

Prior to the discovery of chloramphenicol, typhoid fever was one of the few acute infections for which antimicrobial agents proved disappointing as therapeutic tools

The sulfonamides penicillin, alone or combined with sul fonamides streptomycin, polymyxin, oxytetracycline chlor tetracycline chloramphenicol, and combinations of the latter three have all been used, with greater or lesser fre quency for the treatment of typhoid fever With the exception of chloramphenicol, which is recognized today as the specific treatment, none of these antimicrobials is considered to be clinically effective, except in a few isolated cases This despite the fact that S *typhosa* has been shown to be inhibited *in vitro* by concentrations of all these agents which are easily attainable *in vivo*

Yet while chloramphenicol is considered to be the agent of choice for typhoid fever nevertheless clinical relapses and persistence of positive bacteriological findings during and after chloramphenicol therapy are by no means isolated occurrences. Moreover the typhoid carrier state does not appear to be affected by the drug Thus while chloram phenicol is a useful drug in the treatment of typhoid fever it falls far short of satisfying the criteria for a really specific antimicrobial agent, that is to eradicate completely the infecting organism.

Several interesting observations have been noted in connection with patients having typhoid fever treated with chloramphenicol and showing either clinical or bacteriological relapse. First, within two to three days following the institution of therapy there occurs a dramatic defervescence of temperature, accompanied by symptomatic clinical improvement. Second, blood and stool cultures continue to harbor typhoid bacilli despite the presence of adequate antibiotic concentrations in the blood and probably in most body fluids. Finally even after prolonged chloramphenicol therapy the organisms which continue to persist show no evidence of developing increased resistance to chloramphenicol. This would suggest that either some of the bacilli are inaccessible to the drug, or that they are in some way protected from the action of the antibiotic.

In an effort to overcome these therapeutic failures attempts have been made to improve upon the treatment regimen used. Smadel and associates indicated that in their cases relapses occurred only in patients who received chloramphenicol for less than eight days Consequently they recommended that the treatment course be extended beyond that interval of time. Other investigators however using extended periods of therapy for two weeks or longer continued to report relapses at the same or higher rates More recently evidence has accumulated to indicate that the relapse rate is reduced when therapy is given on an intermittent or discontinuous basis in conjunction with cortisone

Continuous Therapy

Initially a dose of 50 mg per kg of body weight is given orally Subsequent doses consist of 0.5 to 0 75 Gm every six hours or 1 Gm. every eight hours Continue until temperature becomes normal and remains so for forty-eight

hours Subsequent dosage should be 2 Gm. per kg of body weight, divided into four equal doses until the total therapeutic course extends for a total period of fourteen days

Intermittent Therapy

Oral administration with the initial dose approximately 50 mg per kg of body weight. Continue with 1 Gm. every eight hours for a period of five to seven days Discontinue antibiotic for a period of five days Then, repeat original regimen for an additional five to seven days Thus chloramphenicol is administered for a total of ten to fourteen days during a period of fifteen to nineteen days

Some workers in an effort to reduce the incidence of relapses employ typhoid vaccination concurrently with specific chloramphenicol therapy If this procedure is followed, 0 1 cc. of typhoid vaccine is given subcutaneously for eight days beginning on the third day following that on which temperature returns to normal.

In patients with severe toxemia amelioration of this condition may be accomplished by intramuscular or oral administration of cortisone acetate concurrently with chloramphenicol. The initial dose is 300 mg followed by doses of 100 mg every six hours for two doses for a total dose of 500 mg. Under no circumstances should the hormone be given without simultaneous chloramphenicol treatment.

As pointed out previously chloramphenicol therapy alone has not significantly altered the incidence of complications notably intestinal perforation and hemorrhage, formerly seen in typhoid fever When intestinal perforation occurs, immediate surgical intervention is not as imperative as in the preantibiotic era. The reasons for this are (a) that generalized peritonitis can now be more successfully managed with antibiotics and (b) surgical intervention even under

ideal conditions in typhoid fever with peritonitis is still accompanied by high mortality Thus if perforation occurs chloramphenicol should be continued but supplemented with one of the tetracyclines. If these attempts at localization do not appear to be successful, as judged by febrile response and findings of appropriate laboratory studies resort to surgery is indicated. Surgical intervention in order to establish drainage, may still be required even if localization occurs. It is also well not to overlook the supportive measures which are usually indicated in peritonitis

With respect to infections caused by *Salmonella* other than the typhoid bacillus chloramphenicol is not the drug of choice. This is due to the fact that, among the 200-odd *Salmonella* serotypes, there exists a considerable variability as regards susceptibility to antibiotics Thus in salmonellosis in general, one should use either chloramphenicol or one of the tetracycline agents. Dosages of 2 Gm. daily in four divided doses are usually sufficient, with therapy extending for periods of five to fourteen days Streptomycin and the sulfonamides are generally ineffective

Amebiasis

While the management of amebiasis includes supportive therapy prophylactic measures and administration of specific amebicidal drugs no attempt is made in this discussion to evaluate the relative merits of all of these measures in this disease We will confine ourselves specifically to the last of the three factors mentioned above and more specifically the role of antibiotics in the treatment of this disease

Of all the clinically available antibiotics there appear to be only three which can be said to show evidence of having a direct effect upon pathogenic amebae These are chlortetracycline oxytetracycline and fumigallin Additionally

carbomycin has been reported to have amebicidal properties although the evidence for this so far is inconclusive. McHardy and Frey summarized the results contained in available reports on the efficacy of antibiotic treatment in amebiasis According to their data, the failure incidence with the various antibiotics is least in the instances of the three antibiotics mentioned above, namely chlortetracycline, oxytetracycline and fumigallin these incidences being 16 6 8.5 and 14.0 per cent respectively It can be stated, moreover that despite persistent references relative to the value of chlortetracycline in the treatment of amebiasis there can be no question that this agent shows definite limitation as a true amebicidal compound. It is felt moreover that the frequency and severity of gastrointestinal adverse effects which are associated with the dosages which are required to produce a satisfactory clinical response with this agent are such that too much optimism cannot be expressed for the continued use of this agent in this disease

In the case of oxytetracycline the favorable reports have been more consistent and persisted for longer periods of time It would appear that oxytetracycline is an efficient amebicide despite significant side-effects and a definite recurrence rate which would indicate that enthusiastic ac ceptance should be made with reservations In instances where therapy is not required to be too intensive or too long, some of these undesired side-effects such as diarrhea and stomatitis can be avoided.

Fumigallin a relative newcomer to the family of anti biotics, and produced by an aspergillus species was origi nally considered to be an antiphage agent, relatively devoid of antibacterial and antifungal activity *In vitro* studies indi cated that it possesses amebicidal activity On the basis of the work available to date, fumigallin does not seem to

possess any disturbing effects upon the intestinal bacterial flora The most frequently encountered side-effects are abdominal distention nausea, lower abdominal cramps and mild diarrhea Usually the side-effects are brought under control with the cessation of therapy Fumigallin appears to have greater clinical efficacy as an amebicidal agent than do the tetracyclines The most frequently employed dosage is 30 to 60 mg per day in divided doses three or four times a day for a ten day period.

Summation of Effect of Antibiotics on Amebiasis

All of the antibiotics have at one time or another been used in the treatment of amebiasis Only chlortetracycline, oxytetracycline and fumigallin appear to have some direct amebicidal activity on the basis of clinical experience associated with their use. When one considers the duration of the follow-up period which is so essential to the evaluation of any drug for clinical use, then it would appear that oxytetracycline is undoubtedly the drug of choice at this time although fumigallin is quite promising Chlortetracycline is considerably less efficient. Fumigallin requires additional study before its ultimate status in amebiasis can be fully assessed.

SHIGELLOSIS (BACILLARY DYSENTERY)

The causative agents of shigellosis, or bacillary dysentery are gram-negative, nonmotile bacilli belonging to the genus *Shigella*. These organisms produce in humans diarrhea of varying severity On the basis of serological and biochemical differences, *Shigella* organisms are classified into four main groups. Group I includes the classical *Sh dysenteriae* (Shiga bacillus) as well as *Sh ambigua* and members of the Large-

Sachs group Group II designated at present as *Sh. flexneri*, consists of the types heretofore designated as *Sh para dysenteriae* The serotypes formerly known as the Boyd group are now designated *Sh boydii* and comprise Group III Finally *Sh. sonnei* is the only type currently included in Group IV *Shigella dispar* and *Shigella alkalescens* because of their questionable pathogenicity and close relationship to *Escherichia* are no longer included among the *Shigella*.

Sulfonamides specifically sulfadiazine have been used with excellent results in the treatment of shigellosis The sulfapyrimidines, such as sulfamerazine and sulfapyridine have also been found to be efficacious but not to the same extent as sulfadiazine. Surprisingly the poorly absorbed sulfonamides have been disappointing therapeutically probably due to the fact that these agents do not gain access to the regional lymph nodes and deeper layers of the intestinal wall where the bacilli are known to lodge.

Among *Shigella* it is not uncommon to encounter organisms which are sulfonamide-resistant. This is more likely to be the experience when the causative organism is a *Sh sonnei* type rather than a type belonging to the *Sh flexneri*, or *Sh. boydii* groups Streptomycin, chloramphenicol, chlortetracycline and oxytetracycline depending upon individual circumstances have proven effective in such situations While there are reports of the successful treatment of shigellosis with polymyxin B the toxicity of this drug should be a deterrent to its use whenever other agents are available. Supportive measures to maintain fluid and electrolytic balance should not be overlooked, in view of the dehydration which accompanies the disease

TABLE 10

ANTIGENIC SEROGROUP AND INCIDENCE OF SALMONELLAE AT THE PHILADELPHIA GENERAL HOSPITAL (BLOCKLEY DIVISION) 1949 1953

Serogroup	*Type*	*Number of Cases*
B	S *typhimurium*	24
	S *derby*	7
	S *schottmuelleri*	1
C_1	S *cholerae suis*	23
	S *tennessee*	5
	S *oranienburg*	4
	S *montevideo*	4
	S *bareilly*	1
	S *daytona*	1
C_2	S *newport*	8
	S *muenchen*	1
	S *manhattan*	1
	S *litchfield*	1
D	S *enteritidis*	4
	S *panama*	1
E	S *give*	3
	S *anatis*	3
	S *newington*	1

TABLE 11

Guide to Selection of Antibiotics in Therapy of Gastrointestinal Infections

Disease	*Drug of Choice + Dosage*	*Other Useful Agents*
Bacillary dysentery	Sulfadiazine—4 Gm. initially 1 Gm. every six hours for five days.	Chloramphenicol, tetracyclines, polymyxin B, bacitracin
Typhoid fever	Chloramphenicol—50 mg./kg initially 0.75 Gm. every six hours until temperature remains normal for two days. Reduce dose to 0.5 Gm. every six hours and continue until total course is fourteen days. Intermittent therapy—chloramphenicol initial dose 50 mg./kg then 1 Gm. every eight hours for five to seven days. Discontinue for five days. Repeat original regimen for five to seven days.	
Salmonellosis	None	Chloramphenicol, tetracyclines.
Intestinal amebiasis	None	Fumigallin or oxytetracycline.
Extraintestinal amebiasis	None	None
Tuberculosis of bowel	Streptomycin—1 Gm. intramuscularly every three days PAS 12 Gm. per day orally for at least six months.	Isoniazid in conjunction with streptomycin or PAS
Ulcerative colitis and regional colitis	None	Many for controlling secondary infection.

TABLE 11 *(Continued)*

Disease	*Drug of Choice + Dosage*	*Other Useful Agents*
Peritonitis	None	Penicillin and streptomycin tetracyclines.
Biliary Infections	None	Streptomycin, penicillin, tetracyclines.
Hepatitis	None	Tetracyclines.
Weil's Disease	None	Penicillin and chlortetracycline.
Pancreatitis	None	Tetracyclines.

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Antimicrobial Therapy of Specific Infectious Diseases (Continued)

CARDIOVASCULAR INFECTIONS

Bacterial Endocarditis

In the presence of a bacteremia one of the commoner sites for pathogenic organisms to localize and produce metastatic infection is the endocardium of the valve leaflets Under the term bacterial endocarditis are included a variety of clinical syndromes, some of which pursue a rapid and acute course, whereas others evolve slowly over a period of many months Whether the endocarditis is termed acute or subacute depends largely on the nature of the infecting organisms

Acute Bacterial Endocarditis

Acute bacterial endocarditis is usually seen as a complication of one of the acute infectious diseases such as pneumonia meningitis, or gonorrhea, but may occur during the course of a bacteremia in which the primary focus is often unknown such as staphylococcemia. Unlike subacute endocarditis which usually is superimposed on previously damaged valves acute bacterial endocarditis frequently occurs in a normal heart valve Within recent years, we have been seeing an increasing number of cases of acute bacterial endocarditis following cardiac surgery and, occasionally

as a result of contamination during cardiac catheterization. In view of the comparatively greater virulence of the organism in acute infectious endocarditis a more foudroyant course may be expected than in the subacute variety Some of the cases are *so rapidly fatal that they have earned the* title of malignant endocarditis Prior to the advent of the antimicrobial agents only an occasional patient was reported to have recovered from this disease. Many cases are doubtless undiagnosed at present, the affliction being successfully eradicated during the treatment of the primary disease The pathogenic organisms are usually the gonococcus *meningococcus beta hemolytic streptococcus, pneumococcus* staphylococcus albus and aureus influenza bacillus or other virulent pathogens The success of treatment, therefore, is dependent on the susceptibility of the offending organism and the detection and eradication of the primary focus of infection. Excluding certain strains of staphylococci, infections due to cocci are best treated with aqueous penicillin G intramuscularly 200 000 units every three hours for approximately twenty-one days *In vitro* sensitivity studies are indicated especially when staphylococci, or other pathogens are found in the circulating blood, thereby assisting in the selection of the drug of choice Excellent results have been obtained with either tetracyclines oxytetracycline or chloramphenicol, 2 to 4 Gm. daily for three to four weeks in penicillin resistant infections Neomycin 0.5 Gm every six hours intramuscularly for fourteen to twenty-one days has proven a life-saving measure in certain drug resistant infections such as by *Pseudomonas aeruginosa*

Subacute Bacterial Endocarditis

Any individual with valvular or congenital heart disease is a potential case of subacute bacterial endocarditis. In

view of the nature of this disease early and accurate diagnosis followed by the proper use of the antimicrobial agents is of utmost importance. One of the most important steps in arriving at a diagnosis of subacute bacterial endocarditis is to recognize and note the early symptoms of the disease Certainly a history of a recent tooth extraction urological instrumentation or any other surgical procedure especially of the heart bowel, and rectum, followed by symptoms of toxemia, such as fever malaise, easy fatigue loss of energy unexplained tiredness joint or muscle pains as well as such cardiac symptoms as shortness of breath and rapid heart action should suggest this diagnosis In addition, a thorough physical examination and the employment of selected laboratory tests with findings of petechiae (Osler s nodes) a palpable spleen, clubbing of the fingers, tachycardia, changing heart murmurs, neurological abnormalities elevated sedimentation rate and microscopic hematuria are indicative of subacute bacterial endocarditis. Although several positive blood cultures constitute the only definitive basis for unequivocally establishing the diagnosis in about twenty five per cent of cases the causative organism is not recovered from the circulating blood. Certainly the chances of obtaining a positive blood culture are better when the blood samples are taken four to six times during a single twenty four hour period rather than a single sample daily for a week. Furthermore, cultures of bone marrow aspirations will occasionally prove positive in the presence of negative blood cultures and are worthy of trial, conditions permitting.

The selection of the proper antibiotic in the treatment of subacute bacterial endocarditis depends largely on the identity of the infecting organism Where the organism has been isolated and sensitivity tests performed the choice of antibiotic is not difficult In those cases in which the organism

has not been isolated, one is confronted with the problem of how long to delay before starting antibiotic therapy Certainly all patients with valvular heart disease having an unexplained fever for ten days should be treated as a case of subacute bacterial endocarditis Obviously the presence of embolic phenomena demands therapy within a shorter interval of time.

In most cases of subacute bacterial endocarditis penicillin alone or in combination with other antibiotics will prove successful Although there are recorded successes with the wide spectrum antibiotics—chloramphenicol and members of the tetracycline family—it must be remembered that these agents are essentially bacteriostatic (in concentrations which can be tolerated for prolonged intervals of time) while penicillin and, to a lesser extent, streptomycin, are bactericidal under similar conditions The majority of cases of subacute bacterial endocarditis are due to *Streptococcus viridans* which is usually sensitive to penicillin. In a not insignificant number of cases of subacute bacterial endocarditis however the offending organism is an enterococcus most frequently *Streptococcus fecalis* This organism is usually refractory to the activity of penicillin alone, but sensitive to the action of penicillin in combination with streptomycin. Penicillin resistant staphylococci occasionally are associated with a small number of cases and in such instances erythromycin alone or in combination with penicillin or a wide spectrum antibiotic, may have to be employed. Coliforms and other bacterial species are rarely incitants, but when they occur selection of specific therapy is best based on sensitivity test results.

Thus far sufficient data are lacking for a final definition of the optimum dosage of penicillin for this disease. Furthermore, the bacterial sensitivity procedure as performed rou

tinely is at best, but a rough estimate as to dosage. However in most cases due to the *Streptococcus viridans* aqueous penicillin G 200 000 units intramuscularly every three hours for thirty five days will usually prove effective (the potassium salt of penicillin is preferable to the sodium salt if congestive failure is present)

Although we still employ relatively long courses of anti biotic therapy other investigators have reported success with shorter courses of fourteen to twenty-one days Certainly longer courses are indicated for secondary infections or relapses In general, the temperature chart is a reliable guide as to therapeutic response however in the later weeks of treatment an irregular fever may result from drug sensitiv ity Likewise emboli do not necessarily imply continued bac terial activity since, even when the infection is arrested, these may occur at any time in the first one to three weeks of treatment. Oral and repository forms of penicillin for the most part are inadequate and should not be used. In some instances one is forced to employ antibiotics other than penicillin but before doing so it is important to keep in mind the fact that not infrequently the desired results may be obtained by increasing the dose of penicillin. In cases due to enterococci, we recommend massive doses of penicil lin, one million units intramuscularly every three hours a combination containing 0.5 Gm. each of streptomycin and dihydrostreptomycin intramuscularly every twelve hours, plus benemid 0.5 Gm. by mouth every six hours. In our experience it seems advisable to continue this schedule for at least thirty five days, although bacteriological cures and clinical remissions have been obtained within two to three weeks. Where the etiology is such as to contraindicate peni cillin or penicillin plus streptomycin one of the tetracycline group of drugs 2 to 4 Gm. daily by mouth for thirty five

days is worthy of trial. With this form of therapy relapses are common and not infrequently patients develop toxic manifestations requiring discontinuance of the drug Bacitracin, which is synergistic with penicillin against gram-positive organisms, is also helpful in selected cases The dose is 100 000 units intramuscularly daily in four divided amounts

In our experience, we have found that estimation of the intensity of penicillin or penicillin-streptomycin, therapy to be used in a specific case from which isolation of the causative organism has been accomplished, is greatly facilitated by determining the total inhibitory activity exhibited by a patient s serum against the isolated organism before and after therapy is started. The procedure used to determine this total inhibitory activity is as follows (1) The organism is isolated, identified, and maintained in the laboratory Serial dilution tests indicating the concentration of antibiotic required for bacteriostasis as well as for 100 per cent lethal effect are performed. (2) The serum from a clotted specimen of the patient s blood, before antibiotics are started, is serially diluted and tested for inhibiting activity static and cidal, against the specific organism. (3) Therapy is instituted at dosages which, on the basis of clinical experience are deemed adequate Allowing two to three days of continuous therapy so that the patient is stabilized insofar as antibiotic absorption and excretion are concerned, another clotted specimen is drawn. The serum from this specimen is examined in the same manner as the pre-therapy serum. If the intensity of the therapy is adequate the patient's serum should be lethal for 100 per cent of the organisms in a dilution of at least 1 8 or higher If this level of bactericidal activity is not observed, the antibiotic dosage is increased empirically and the test repeated about a week

later By this means it is possible to follow the lethal activity of the serum at regular intervals using the results of the tests as a guide to altering the amount of antibiotic being prescribed It is recommended that it be determined through the use of penicillinase whether the lethal effects observed are due to penicillin or to some peculiarity of the patient's serum Additionally it is also possible to differentiate by using penicillinase, what portion of the inhibitory serum activity is due to penicillin and streptomycin in those instances where the combination is being employed.

In those cases in which the organism has not been isolated, one is confronted with the problem as to what form of antimicrobial therapy should be instituted. In such cases, one must asume that the causative organism is relatively resistant to penicillin therapy and it is advisable to employ the schedule as outlined above for cases due to the enterococcus Obviously if after five to seven days of this regime there is no clinical improvement, then one is obliged to make another choice of drug, or drugs In such cases there is no alternative but to resort to the method of trial and error

Eradication of Possible Foci of Infection

Since certain focal infections may cause a reinfection of the heart valves it is important that a careful search be made for possible foci of infection and their eradication effected if possible This is best done while the patient is receiving antimicrobial therapy Since the upper respiratory passages and mouth particularly the teeth, harbor foci which act as the commonest portal of entry in this disease it is important that every patient have a thorough check of the ears, paranasal sinuses, tonsils gums and teeth. In those cases which have followed urological instrumentation, the

same precaution holds Furthermore, since subacute bacterial endocarditis may result from a pre-existing subacute endarteritis one must consider the possibility of a patent ductus arteriosus or arteriovenous aneurysm. Obviously the eradication of possible foci will not cure an established case of subacute bacterial endocarditis but it is imperative that all such foci be eradicated during the time the patient is receiving antimicrobial therapy as a prophylactic measure against recurring attacks Since so many cases give a history of recent tooth extraction and because of the fact that the infection often involves more than one tooth, it seems better to sacrifice an innocent tooth than to jeopardize a life In this connection it should be emphasized that the clinical, pathological, and x ray diagnosis is often masked by antimicrobial therapy thereby making it difficult to decide whether a tooth is diseased or not. Certainly an empty house is better than a bad tenant. Furthermore the ligation of a patent ductus arteriosus and the removal of arteriovenous aneurysms are indicated. The development of mycotic aneurysms must be suspected in obstinate cases This complication is a serious one and demands surgical extirpation The development of pain and a mass with or without pulsation leads one to this diagnosis especially when occurring in the extremities Obviously abdominal, thoracic, and intracranial lesions are much more difficult to detect and eradicate.

Nonbacterial Endocarditis

The chief cause of nonbacterial endocarditis is acute rheumatic fever and it is usually seen as part of acute rheumatic carditis Penicillin orally 200 000 units daily (or sulfadiazine 0 5 to 1.0 Gm. daily by mouth, if penicillin cannot be used) is employed prophylactically

Myocarditis

Although many cases of myocarditis are the result of non infectious agents for example senile degeneration and hyper tension, there are many cases which are due to specific infections some of which are amenable to antimicrobial therapy Diphtheria, typhoid fever pneumonia, typhus and meningitis are a few examples In most instances whatever damage to the heart occurs is usually not too severe since very few deaths are attributable to this complication *per se* Furthermore, there are probably other instances in which an acute myocarditis has developed during an infectious illness and manifests itself months or even years later Certainly this is true in many so-called cured cases of subacute bacterial endocarditis Since acute myocarditis is usually associated with a systemic disease, the diagnosis and choice of therapy are apparent. Most cases of chronic myocarditis are of unknown etiology However such infections as tuberculosis have been shown to give rise to this condi tion and in most instances there is evidence of tuberculosis elsewhere in the body

Pericarditis

Pericarditis is almost always secondary to some other primary infection within the body as any generalized sepsis may localize in the pericardium Fortunately with the wide spread use of the antimicrobial agents pericarditis is not a common complication although it is quite likely that many cases do occur but go unrecognized. However acute peri carditis is seen occasionally following such diseases as pneu monia complicated by empyema caused by various pyogenic organisms especially the pneumococcus and hemolytic streptococcus In addition, tuberculous pericarditis is also seen secondary to tuberculosis of the pleura lungs or mediastinal

glands For the treatment of acute pericarditis the selection of the proper antimicrobial agent is dependent upon the general infection For the most part, it is well to employ large doses of the drug over a relatively long period of time. Certainly a number of acute cases are successfully handled with antimicrobial therapy alone, but some will require surgical intervention because of the development of adhesions thus giving rise to a chronic adhesive pericarditis Since excessive fluid may accumulate in the pericardial sac, giving rise to cardiac tamponade it is necessary in such cases to perform a pericardial puncture The advisability of reinjecting antibiotics after the removal of fluid is still a controversial matter

For the treatment of tuberculous pericarditis see page 88

VENEREAL DISEASES

Fortunately the venereal diseases syphilis gonorrhea, lymphogranuloma venereum, chancroid, and granuloma inguinale are all susceptible to antimicrobial therapy Despite this the incidence of venereal diseases continues to be high and, although one often hears optimistic expressions of opinion concerning their disappearance and relegation to the minor status now shared by such dreaded diseases as small pox and diphtheria, this appears at present to be based on wishful thinking rather than observation. Nevertheless this group of diseases is rapidly yielding to drug therapy especially in this country

Syphilis

Syphilis if recognized early and treated intelligently can be controlled in close to 100 per cent of cases Penicillin is considered the drug of choice in the initial treatment of all types of this disease owing to its high percentage of favor

able responses ease of administration low cost, and relatively short period of treatment. Furthermore penicillin reactions are rare and are seldom of such severity as to necessitate interruption of therapy The most important is the Herxheimer reaction which is usually manifested by fever during the first twenty four hours of treatment, often with aggravation of the syphilitic lesions and such symptoms as headache, malaise, chilliness and weakness This reaction apparently signalizes the effectiveness of treatment, since it is ascribed to the abrupt, massive destruction of *T pallidum* in the lesions and blood stream and does not constitute an indication for interruption or discontinuance of penicillin therapy except when the reaction is severe or in the presence of hoarseness or tinnitus Usually this reaction will subside spontaneously within twenty four to thirty six hours The Herxheimer reaction is observed most frequently in the treatment of primary and secondary syphilis although it may occur in latent cases in which it may represent an extremely dangerous situation and must be guarded against. Special caution is particularly important in cases of cardiovascular syphilis as any untoward reaction (therapeutic paradox) is not without serious consequences Fortunately the number of therapeutic shocks and paradoxes following penicillin has been extremely small, particularly since the advent of more refined preparations of the drug As a result, many syphilologists especially in this country have abandoned all preparatory treatment, although most British authorities continue to employ bismuth and iodides prior to penicillin therapy of cardiovascular syphilis

In addition to penicillin chloramphenicol and the tetracyclines have been shown to have definite value as antisyphilitic agents for primary or secondary syphilis, although their effectiveness is definitely inferior to penicillin. How

ever the use of one of these broad spectrum agents may prove valuable in patients who are sensitive to penicillin and who can be kept under supervision, especially if chlor amphenicol is selected.

Primary and Secondary Syphilis

Successful treatment of acute syphilis (primary or second ary) is dependent upon maintaining a continuous penicil lemia for at least ten days This is best accomplished by procaine penicillin in oil with two per cent aluminum monostear ate 1,200 000 units intramuscularly every three days procaine penicillin in oil with two per cent aluminum monostearate 600 000 units daily for eight days. Cases failing to respond to one of the above schedules should be given a second course of penicillin alone, employing larger total dos age (twenty per cent or more increase) over a period of ten to fifteen days or combined with a course of heavy metals arsenicals and bismuth. Not infrequently an apparent failure to respond to initial penicillin therapy represents a reexposure and reinfection, hence the importance of investigat ing all failures from an epidemiologic standpoint. At this time promising results are being obtained with a single intra muscular injection, 2,400 000 units of Benzathine Penicillin G Although oral penicillin has been used with reported suc cess by some workers in early syphilis it is not recommended The usual total dosage for chloramphenicol or one of the tetracyclines is 60 Gm. administered as 2 to 4 Gm daily in divided doses

Latent and Late Syphilis

For the most part, early and late latent syphilis are successfully treated with procaine penicillin 600 000 units daily for ten days and if relapses occur the therapy is repeated.

The treatment of late syphilis—tertiary mucocutaneous, osseous neural, and especially cardiovascular involvement—demands a careful selection of patients as regards age sex, duration of illness and general physical condition For the most part, no treatment is given to individuals over sixty years of age who have had syphilis for more than thirty years or are suffering with other disease conditions which would markedly reduce life expectancy Furthermore in cases in which a Herxheimer reaction or therapeutic paradox is to be avoided, treatment with bismuth is still recommended by many investigators for six to twelve weeks before instituting penicillin In general, the penicillin therapy of late syphilis embraces procaine penicillin 600 000 units daily for ten to fourteen days If this fails the same schedule of penicillin is repeated alone or in combination with arsenic and bismuth injections Cases of cardiovascular syphilis are best prepared with bismuth injections and potassium iodide orally for twelve weeks before penicillin treatment, although this preparatory therapy has been abandoned in many clinics

Neurosyphilis

Therapy of neurosyphilis is governed by the stage at which the condition appears. According to most syphilologists, penicillin is the drug of choice although in stubborn cases it is often combined with the heavy metals and, in the late stages with fever therapy A minimum schedule of procaine penicillin, 600 000 units daily for fourteen to twenty-one days is generally adequate

Syphilis in Pregnancy

During the first five months of pregnancy procaine penicillin 600 000 units daily for twelve injections will prevent

syphilis in the fetus in most instances After the fifth month, penicillin G in aqueous solution, 100 000 units intramuscularly every three hours for ten days

Congenital Syphilis

Penicillin alone represents the therapy of choice, regardless of the age or severity of the disease. For early congenital syphilis penicillin G aqueous, 200 000 units per pound of body weight is given intramuscularly in divided daily doses every two hours for ten days. In late cases procaine penicillin 100 000 units daily for ten days is recommended. Therapeutic failures will usually respond to retreatment with larger doses of penicillin, doubling the original dosage and continuing for twenty-one days

GONORRHEA

Penicillin in adequate amounts will prove successful in practically all cases of uncomplicated gonorrhea. Procaine penicillin 600 000 units intramuscularly is usually sufficient for acute cases in males in chronic cases and females it is best to repeat the dose at twenty four and forty-eight hours So-called penicillin resistant cases are usually effectively treated with aqueous penicillin G intramuscularly 50 000 units every three hours for twenty injections The tetracyclines and chloramphenicol are all useful agents in the treatment of gonorrhea and are recommended in patients sensitive to penicillin and in the occasional refractory case With any of these wide spectrum drugs 2 to 4 Gm. in divided doses every six hours is advisable. Complications, such as arthritis are best treated with penicillin as outlined above for resistant cases

Lymphogranuloma Venereum

The tetracyclines are useful in all stages of lymphogranuloma venereum with the degree of effectiveness depending on the type and degree of involvement. In early cases with minimal tissue breakdown the results are optimal while in cases complicated by fibrosis and fistulae they act as adjuncts to surgery With any member of the tetracycline group the usual dosage should be 250 to 500 mg every six hours for thirty days

Granuloma Inguinale

Streptomycin and the wide spectrum antibiotics are all highly effective in the treatment of granuloma inguinale Streptomycin intramuscularly 1 Gm. every six hours for ten days represents the therapy of choice A febrile response for several days is not unusual and occasionally a transient urticaria, or erythema, will appear One of the tetracyclines 500 mg orally every six hours for ten days may be used especially in streptomycin resistant cases

Chancroid

Many authorities still consider the sulfonamides as the drugs of choice in this disease in that they are highly effective and do not mask syphilis Sulfadiazine orally 3 Gm. initially followed by 1 Gm every six hours for seven days if buboes are present, treatment is continued an additional seven days. The tetracyclines are also effective 500 mg every four to six hours for ten days Should a fulminating phagedenic chancroid develop aqueous penicillin G 50 000 units intramuscularly every three hours is indicated, as such a complication is usually accompanied by fusospirochetosis

Soap and water and common sense are the best disinfectants
Sir William Osler (1849–1919)

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TUBERCULOSIS

An ideal therapeutic agent capable of destroying the tubercle bacillus within the tissues of Man is as yet not available Nevertheless tremendous advances in drug therapy of tuberculosis have occurred during the past decade. As a result, the mortality rate has markedly declined, the prognosis is strikingly improved, a broader surgical attack has become feasible and, if public health measures were adequate it would probably be possible to eradicate tuberculosis

At this time three antituberculous drugs streptomycin para aminosalicylic acid (PAS) and isoniazid (INH) constitute the most proven agents for the treatment of tuberculosis Other drugs such as oxytetracycline, viomycin, neomycin, thiosemicarbazone, and pyrizonamide have been shown to possess antituberculous activity and may be useful when the drugs of choice are contraindicated. Also certain adjuvants in antimicrobial therapy of tuberculosis have been developed but their place in the total picture has not been clarified. Benemid, administered in conjunction with PAS by mouth may cause some elevation and prolongation of PAS blood levels but no impressive advantages have been demonstrated for its use Polyvinyl pyrralidone has been employed for the same purpose in the intravenous administration of PAS and may have some virtue occasionally in that it permits PAS to be given in small doses by syringe injection and obviates the need for an intravenous drip Tuberculin has been used as an adjunct intrathecally in the treatment of far advanced cases of tuberculous meningitis with reported success in a few instances This material is administered in increasing doses in order to produce a lysis of meningeal exudate with consequent liberation of

intracellular tubercle bacilli so that the antituberculous agents may better attack the microorganism ACTH and cortisone have also been employed with success in critical cases of tuberculous meningitis and, although in dosages used at present they may well depress the defense mech anisms of the body so that the tubercle bacillus can spread more easily to other parts of the body the possibility re mains that a suitable dosage regimen may yet be developed so that these hormones can be used to advantage in com bination with antimicrobial drugs in the treatment of tuber culous meningitis. Certainly at this time tuberculin, ACTH and cortisone must be more extensively evaluated before they are considered proven adjuncts in the treatment of tuber culous meningitis

Streptomycin represents the sheet anchor of antimicrobial therapy of tuberculosis, although there are two disadvan tages associated with its use in this disease. Tuberculosis being a relatively chronic disease it requires prolonged treat ment, which leads to an increased incidence of drug toxicity The second disadvantage lies in the frequency with which tubercle bacilli develop resistance to streptomycin. For tunately both of these disadvantages have been minimized with the discovery that streptomycin, given every third day is just as effective as when it is administered daily which regimen results in a lower incidence of toxic reactions as well as in smaller incidence of bacterial resistance (eighty two to sixty-seven per cent) Furthermore when strepto-mycin is combined with PAS or INH there is an additional reduction in the incidence of bacterial resistance to strepto-mycin

In general, the treatment of all types of tuberculosis is similar in that it requires extension over comparatively long periods of time However certain forms of the disease re

spond more dramatically than do others depending on the degree with which necrotic material may slough into the environment and the acuity of the pathological reaction. Ulcerative lesions which communicate freely with the environment, such as mucosal lesions (ulcers in the respiratory or gastrointestinal tracts for example) are able to discharge their necrotic contents readily and healing thus takes place more rapidly The acuity of the pathological reaction is perhaps the major determining factor in the rapidity of response to antituberculous treatment. This is true whether the lesion is parenchymal, mucosal, or serosal.

Pulmonary Tuberculosis

Tuberculosis of the lungs constitutes more than ninety per cent of all tuberculous lesions in this country and does not respond as rapidly to drug therapy as certain other forms of the disease such as tuberculous pneumonia and the endobronchial and laryngeal forms At the present time, the therapeutic regimen of choice for the average case of streptomycin sensitive pulmonary tuberculosis is streptomycin 1 Gm intramuscularly two to three times weekly combined with 12 Gm. daily (in three divided doses) of oral PAS or isoniazid 150 to 300 mg daily (in three divided doses) by mouth. In severely ill patients or in cases of tuberculous pneumonia, streptomycin should be given in 1 Gm. daily doses which may be reduced depending on the clinical response Other effective therapeutic regimens include streptomycin 0.5 Gm. or 1.0 Gm. daily plus PAS *Streptomycin resistant cases are probably best treated with* INH, 150 to 300 mg. by mouth per day combined with PAS The duration of therapy for pulmonary tuberculosis is largely dependent upon the extent of the disease and the degree of cavitation. At this time it appears that the longer a patient

with pulmonary tuberculosis is treated with drugs the better are the results although the rapidity of improvement usually begins to decrease after the first six months of treatment Nevertheless in some cases, continued treatment for several years has resulted in striking but gradual improvement of the disease The most recent concept teaches that a patient should be treated for six months after the target point has been reached For most patients this means twelve to eighteen months of uninterrupted therapy In cases requiring surgery for cavities which fail to close within five to eight months antituberculous therapy is usually continued for an additional twelve months If however it is not possible to cure (closure of cavities, conversion of sputum, and stabilization of the process) the patient on such a program, it may be advisable to continue the drugs for an indefinite period of time. This is especially advisable in those patients who have negative sputum and persistent cavitation in that it is to be expected that within six months after cessation of drug therapy such patients will have relapsed bacteriologically and again present a positive sputum. At this point, the sputum will contain drug resistant bacteria. The rationale for indefinite treatment in such cases is one based largely on the public health aspect of the disease, since if it is at all feasible, it is desirable to maintain sputum conversion in those patients who cannot be cured for various reasons but cease to excrete tubercle bacilli while on drug therapy In this way contagion can be diminished and the patient s disease usually does not become worse There remains a considerable number of patients who despite prolonged antimicrobial therapy continue to excrete tubercle bacilli into their environment This group of patients remains a serious problem which as yet has not been solved by drug treatment.

Although many cases of tuberculous pneumonia will show almost complete regression within a period of six months, it seems advisable to continue therapy for an additional three to six months as not infrequently residual necrotic tissue remains which sometimes requires more drastic therapy such as resection, in order to avoid relapse In general, the same response to drug therapy is seen in cases of laryngeal, endobronchial, and intestinal forms of the disease, although these often represent complications of pulmonary tuberculosis and require prolonged therapy

Pleural Effusions

Pleurisy with effusion in an otherwise apparently healthy individual must be considered as tuberculous in origin until proven otherwise. Often it is an expression of hematogenous tuberculosis and is frequently followed by pulmonary disease Therefore, all such cases should receive antituberculous drugs for a minimum of six months whether or not a parenchymal lesion is demonstrated by x rays.

Pericarditis and Peritonitis

Serosal forms of tuberculosis, such as pericarditis and peritonitis are almost always acute processes and therefore respond rapidly to drug treatment. However many cases of serosal tuberculosis are complicated by more serious diseases elsewhere in the body and the prognosis depends upon the nature of the more serious forms than upon the serosal lesions and treatment is therefore determined upon the presence or absence of such diseases

Miliary and Meningeal Tuberculosis

These two types of tuberculosis represent the most difficult problems in drug therapy and since they are closely related forms of the disease they are best included in the same discussion The prognosis differs somewhat depending

on whether we are dealing with each form separately or with a combination of the two Miliary tuberculosis has in general a better prognosis than tuberculous meningitis when it occurs without meningeal involvement This is probably because the miliary pulmonary lesions have a pathway for discharge of necrotic material, through the respiratory tract into the environment, if necrosis should occur This, of course is not true of tuberculous meningitis since the disease is confined within a rigid space The treatment of these forms of tuberculosis is still not well defined but, in general the regimen of choice is streptomycin 2 Gm. daily plus PAS 12 Gm and usually INH 200 to 300 mg. daily Treatment is continued for at least one year with the dosage of streptomycin reduced to 1 Gm daily if the response is satisfactory In comatose patients all three drugs are given parenterally until oral administration of PAS and INH becomes feasible Although intrathecal streptomycin (20 to 50 mg. every other day) in tuberculous meningitis is still employed during the initial weeks of treatment by some investigators this procedure is being rapidly abandoned. The ultimate value of intrathecal PPD and ACTH and cortisone in terminal cases of tuberculosis meningitis still remains to be determined. However in those patients presenting clinical and laboratory evidence of adrenal failure one is justified in administering relatively small doses of hydrocortisone (50 to 75 mg daily) in combination with antimicrobial therapy

Genitourinary Tuberculosis

For the most part, the antimicrobial treatment of tuberculosis of the genitourinary tract is the same as outlined for pulmonary tuberculosis Although symptomatic response occurs more rapidly when streptomycin is given daily continuous therapy should be avoided because of the emergence

of streptomycin resistant organisms and drug toxicity In uremic cases the dosage of streptomycin should be halved if it is given daily The conversion rate of urine cultures in patients with renal lesions is well over sixty per cent at the end of eight months and reaches eighty per cent at the end of twelve months of drug treatment. The urine conversion rate is even higher in cases of prostatic tuberculosis, but does not necessarily reflect healing of the foci in the prostate. Patients with pyelographic evidence of renal tuberculosis usually show very little progression of the destructive process even after drug therapy is stopped. The treatment of choice for urine positive unilateral destructive renal tuberculosis and epididymitis continues to be surgery in conjunction with the use of specific antimicrobial agents. Postoperative drug therapy is continued until pyuria disappears.

Other Types of Tuberculosis

The same principles of specific antituberculous therapy apply to the disease wherever it may develop Tuberculosis of the bones and joints usually requires surgical intervention, although when confined to the synovial membrane, medical treatment alone may prove sufficient. Both tuberculous peritonitis and endometritis usually respond well to drug therapy as does lymphadenitis and cutaneous lesions

Antituberculous Agents in Surgery

The surgical management of tuberculous lesions has been markedly altered by the use of these drugs In general, surgery of both pulmonary and extrapulmonary tuberculosis is most likely to be successful if several months of medical therapy is completed before operation. However in cases demanding more immediate surgical intervention, preoperative medical therapy for twenty four to forty-eight hours will provide adequate tissue concentration of the antituberculous drugs to which the bacilli are sensitive.

9

Antimicrobial Therapy of Specific Infectious Diseases (Continued)

MUSCULOSKELETAL INFECTIONS

Arthritis

ACUTE suppurative arthritis can be caused by any pyogenic organism, the most frequent being the gonococcus tuberculosis pneumococcus and staphylococcus Therapy is directed towards the selection of the appropriate antibiotic which is given systemically in relatively large amounts and at times locally into the joint cavity since penetration is poor although massive dosages will usually compensate for this drawback. Against penicillin sensitive organisms aqueous penicillin G 200 000 to 500 000 units intramuscularly every three to four hours plus 50 000 units locally every twenty four hours to forty-eight hours into the joint space as indicated in certain instances The treatment of other types of this disease is determined by bacteriological and sensitivity studies

Osteomyelitis

Most cases of osteomyelitis are caused by the staphylococcus and streptococcus although any pyogenic organism is capable of reaching the bone In general, the treatment of this disease consists of the prompt administration of an

effective antibiotic in early cases This may avoid surgical intervention however the evacuation of confined pus and/or the cleansing out of all infected dead bone are important factors in the successful management of this disease. Penicillin (aqueous penicillin G 200 000 to 500 000 units intramuscularly every three hours) represents the drug of choice for initial treatment before the causative organism has been identified. Subsequent studies may require the use of another antibiotic agent such as erythromycin 200 to 400 mg every four to six hours by mouth or 250 mg every six to eight hours intravenously One of the tetracyclines 500 mg. every four to six hours orally or 100-500 mg intravenously every six to twelve hours is also of value in such cases

INFECTIONS OF THE ORAL CAVITY

For the most part, infections involving the membranes of the oral cavity represent buccal manifestations of systemic diseases or an extension of an inflammatory process from a nearby site. There are, however certain local infections involving the tongue mouth, and gingivae which are amenable to antimicrobial therapy

Glossitis

Although the tongue usually serves as a mirror of infection elsewhere in the body on occasion the disease is primary Painful ulceration of the tongue may represent a streptococcal infection and is best treated with oral penicillin, 250 000 units every four to six hours for five to seven days, or in severe cases aqueous penicillin G *300 000 units* intramuscularly every six to eight hours

Stomatitis

Ulceromembranous stomatitis (Vincent s angina, trench mouth) represents a specific fusospirochetal disease involv

ing the mouth throat, or gums that responds dramatically to antibiotic therapy especially penicillin (procaine penicillin 600 000 units intramuscularly followed in twenty four hours by penicillin oral 250 000 units every six hours for forty-eight to seventy-two hours)

Among the other primary infections of the oral cavity is a nonspecific type of ulcerative stomatitis which may progress rapidly to a gangrenous state and prove fatal if not treated in its early stages Usually this disease is caused by a mixed infection and is best treated with tetracycline or oxytetracycline orally (500 mgm) or intramuscularly (100 mg) every four to six hours, as necessary

Ludwig s Angina

A widespread cellulitis involving the floor of the mouth and usually caused by streptococci or occasionally staphylococci. This disease demands prompt and forceful antimicrobial therapy with aqueous penicillin G 200 000 units every three hours

Dental Infections

Just as in the practice of medicine antimicrobial agents are being used in ever increasing quantities in the field of dentistry Although the management of dental infections belongs primarily in the hands of the skilled dental or oral surgeon there are many instances where the physician is confronted with such problems as they are related to the general care of the patient Certainly the use of antimicrobial agents in such instances demands a close cooperation between the dentist and the physician.

Antimicrobial agents are applicable in the field of dentistry both from a preventive and curative standpoint Prophylac

tically these agents are employed in individuals with valvular or congenital heart disease in whom extraction or surgical drainage is contemplated, in order to reduce the potential hazard of subacute bacterial endocarditis. All such cases should receive penicillin (procaine penicillin 300 000 units intramuscularly) preceding the operative procedure and at twenty four and forty-eight hours afterwards or oral penicillin (250 000 units every four hours) for twenty four hours before and forty-eight hours afterwards Patients unable to tolerate penicillin may be given oxytetracycline or tetracycline 500 mg by mouth every six hours for twenty four hours before and forty-eight hours afterwards Furthermore, the antimicrobial agents are now being used in virtually all cases of major maxillofacial surgery in the belief that this practice has reduced the incidence of infections of the soft tissues and bone.

Therapeutically the antimicrobial agents are being used successfully in a variety of conditions such as root canal sterilizations necrotic pulps abscesses cellulitis Vincent s angina, and localized osteitis or "dry socket" following tooth extraction. For these purposes penicillin and the tetracyclines represent the drugs of choice.

Ocular Infections

With the advent of modern antimicrobial therapy has come a better understanding of the causes of ocular infections and their management. In view of the frequency with which they are encountered in the general practice of medicine and the effectiveness of these agents many especially some of the extraocular infections are being successfully handled by the general practitioner Nevertheless a substantial number of ocular infections are subsequently seen by an ophthalmic

physician because of errors of diagnosis inadequate treatment, or drug complications.

In general, the selection of an antibiotic for the treatment of ocular infections is determined by (1) The sensitivity of the invading organism (2) location and seriousness of the infection and (3) capacity of the drug to induce hypersensitivity While in many instances the nature of the infection is recognized clinically the fact remains that intelligent antimicrobial therapy is dependent upon a bacteriological diagnosis, in order that the appropriate agent, or agents be administered. Whereas the topical application of an antibiotic alone will often successfully eradicate an infection it may be necessary in other instances to administer the antibiotics systemically or by local injections into the eye, or periorbital areas The choice of method for administering antibiotics is determined by the relative capacity of these agents to penetrate or diffuse into the eye In the main, none of the available antibiotics in the dosages commonly employed in the treatment of most systemic infections will not diffuse sufficiently into the eye to produce therapeutically effective concentrations although diffusability is greater in the presence of inflammation For this reason, retrobulbar inoculations direct injection into the globe and subconjunctival injections are frequently necessary Of the currently used antibiotics, penicillin is recognized as the one most frequently inducing hypersensitivity especially when applied topically For this reason plus the relatively high incidence of penicillin resistant staphylococci encountered in ocular infections the tetracyclines erythromycin bacitracin, and polymyxin B are being employed for many types of these infections Furthermore, recent experience indicates that the concomitant local and/or systemic use of hydrocortisone produces more immediate results.

Extraocular Infections

Blepharitis

Squamous, or ulcerative blepharitis, a bacterial infection, is usually caused by the staphylococcus or streptococcus and is treated both locally and systemically with a wide spectrum antibiotic—oxytetracycline or tetracycline (5 mg per Gm. of ointment base, plus 250 to 500 mg every six hours by mouth) As a result of sensitivity studies it may be necessary to employ one or more of the other antibiotic agents.

Conjunctivitis

Infections involving the conjunctivae may be produced by bacteria or viruses and may be either acute or chronic in nature. Most cases of acute bacterial conjunctivitis are produced by *Hemophilus influenzae* (Kochs-Weeks) the pneumococcus the staphylococcus or the gonococcus

Bacterial Conjunctivitis
Ophthalmia neonatorum

A conjunctivitis seen in the newborn, while for a considerable time regarded as being caused, in most instances, by the gonococcus has more recently been shown to have a greater incidence of staphylococcal and pneumococcal etiology although the gonococcus continues to be involved While at the present time the antibacterial agent of choice in the prophylaxis of this disease is controversial, in that many states still require the routine use of silver nitrate, despite the demonstrated effectiveness of penicillin.

In the treatment of ophthalmia neonatorum aqueous penicillin G intramuscularly 3 000 units per pound of body weight, in four equally divided doses daily plus local penicillin, 100 000 units per ml. as drops into both eyes, will prove effective and at the same time will prevent spread of

the infection. More recently the tetracyclines have been used orally and locally with good results.

Adult Gonococcal Conjunctivitis

Adult gonococcal conjunctivitis is usually acquired by self inoculation from a genital infection and is seen most often in doctors and nurses working with gonorrheal patients It is treated in essentially the same manner as outlined above for conjunctivitis neonatorum Aqueous penicillin G 200 000 units intramuscularly every three hours combined with in stillations into both eyes

Conjunctivitis (Other than Gonococcal)

Most cases of acute conjunctivitis due to organisms other than the gonococcus can be successfully treated with local application of one of the tetracycline group of antibiotics (5 mg. per Gm. of ointment base) every four to six hours.

The commonest cause of chronic bacterial conjunctivitis is due to the staphylococcus and is often associated with a bleph aritis with treatment directed toward this latter condition

Viral Conjunctivitis

Although a number of viruses give rise to conjunctivitis, only two produce infections which are known to be amenable to treatment with antimicrobial agents These are trachoma and inclusion conjunctivitis the etiologic agents of which resemble the viruses of pneumonitis psittacosis and ornithosis.

Trachoma

Good results have been obtained in the treatment of this disease with the local or systemic use of the sulfonamides and the wide-spectrum antibiotics especially chlortetracy cline and oxytetracycline The recommended treatment at present for acute cases is chlortetracycline ointment (0.5 per

cent) every six hours for ten days With cases of longer dura tion (four to eight weeks) treatment is required for fourteen to thirty five days *Chronic trachoma requires therapy for* two to three months before complete healing occurs

Inclusion Conjunctivitis

The treatment of this disease is essentially the same as out lined above for trachoma.

Acute Catarrhal Conjunctivitis

As a rule this disease is self limiting, but antimicrobial therapy will shorten its duration and prevent complications Most cases will respond satisfactorily to drops of wide-spec trum antibiotics administered around the clock.

Keratitis

Inflammations of the cornea may be caused by a variety of bacteria among which are the staphylococcus pneumococcus, *Pseudomonas Proteus Hemophilus* tubercle bacillus and the *Treponema* of syphilis In general, treatment is directed at the conjunctivae and lid border and is determined on the basis of identity and susceptibility of the involved pathogen. Combinations of antibiotics and hydrocortisone locally and, in selected cases systemic therapy represent the best form of therapy

Orbital Cellulitis

This disease is seldom primary in that it usually represents an extension of infection from the accessory nasal sinuses or teeth, or metastatic spread from infections elsewhere. Anti microbial therapy in the form of penicillin (aqueous penicil lin G 200 000 units every three hours or tetracycline, or oxy tetracycline 250 to 500 mg every four to six hours by mouth) is indicated.

Cavernous Sinus Thrombosis

Cavernous sinus thrombosis usually represents an extension of an infection from the nasolabial area, nose or orbit and demands prompt and forceful therapy Aqueous penicillin G should be given intramuscularly 200 000 units every three hours In stubborn cases the possibility of a penicillin resistant organism must be considered Erythromycin intravenously 250 mg every six to eight hours is indicated in such instances.

Intraocular Infections

For the most part, intraocular infections are the direct result of traumatic or surgical insult to the eye, although some represent an ocular manifestation of a systemic disease. Regardless of the cause, successful treatment requires prompt and vigorous therapy both systemically locally (topical and intraorbital) The same principles of therapy apply here as outlined above for keratitis However in traumatic cases, the possibility of gas bacilli and tetanus should not be overlooked. Furthermore since most traumatic cases and a number of postoperative infections are due to the staphylococcus, one is justified in starting massive doses of crystalline penicillin G intramuscularly 500 000 to 1 000 000 units every two to three hours Subsequent bacteriological studies may indicate the need for some other antibiotic agent notably erythromycin for penicillin resistant staphylococci

INFECTIONS OF THE SKIN

The advent of the antimicrobial agents has revolutionized the therapy of skin diseases Although penicillin is effective in many of these infections its use topically is not recommended because of its allerginicity There are other more effective antibiotics for local treatment, especially in mixed

infections namely bacitracin polymyxin, and neomycin. Recently combined hydrocortisone-antibiotic therapy has produced beneficial effects in certain stubborn infections of the skin.

Impetigo

Most cases of impetigo will respond to local applications of neomycin or bacitracin ointment. To patients with extensive lesions and those who fail to respond to local therapy within forty-eight hours tetracycline or oxytetracycline 250 to 500 mg every four to six hours should be given.

Furuncles and Carbuncles

Staphylococcal infections of the skin are a common occurrence and, unless the lesion or lesions are not numerous or deep-seated, conservative treatment alone is often sufficient. However in patients with diabetes mellitus those in which the lesion is situated in the nasolabial area, on the nose or beneath the eye and in those in which conservative measures have failed, treatment with antibiotics should be carried out promptly Procaine penicillin, 300 000 to 600 000 units daily or if the infection is severe, aqueous penicillin G 100 000 units every three to four hours Bacitracin ointment may be used topically as an adjunct to systemic therapy Erythromycin, 400 mg every four to six hours is indicated if the response to penicillin is not satisfactory However sensitivity studies should be carried out, if possible, in order that therapy may be adjusted properly As with other localized pyogenic infections these drugs are not to be used as substitutes for surgical drainage

Erysipelas

This streptococcal disease usually responds most readily to penicillin (procaine penicillin 300 000 to 600 000 units

daily) or in penicillin sensitive patients sulfadiazine (1 Gm every four to six hours) Either drug should be continued until the patient has been afebrile for three days

Pemphigus

The antimicrobial agents are ineffective in the treatment of all types of pemphigus (vulgaris foliaceus vegetans) and are of value only for control of superimposed bacterial infection Since cortisone and ACTH constitute the best treatment for pemphigus but their use is associated with lowering of resistance to infection if would seem advisable to administer antibiotics *e g* tetracycline or oxytetracycline 250 to 500 mg. every four to six hours

Acne Vulgaris

Although the staphylococcus and acne bacillus apparently assume some role in this disease, it appears that the antimicrobial agents are of limited usefulness and are employed for relatively short periods of time only in severe cases or at the time of operative procedures Tetracycline or oxytetracycline 250 to 500 mg every four to six hours for five to ten days

MISCELLANEOUS INFECTIONS

Brucellosis

Brucellosis (undulant fever) may be caused by *Brucella abortus melitensis* or *suis* In cases of acute Brucellosis, present day experience indicates that the treatment of choice is represented by a combination of streptomycin hydrostreptomycin, and oxytetracycline administered for at least three weeks The streptomycins are given intramuscularly 1 Gm (0.5 Gm. of each) every twelve hours for the first seven to ten days and then, depending on the response may be reduced to

1 Gm. daily The dosage of oxytetracycline is 500 mg orally every four to six hours for an equivalent period of time and may be reduced subsequently to one-half of this dosage, if indicated Not infrequently therapy is followed by a secondary rise in temperature especially in debilitated patients who have suffered with the disease for a long time and presents no reason for concern or cause for changing therapy Relapses may occur and require additional therapy In seriously ill patients adjuvant *cortisone therapy may be helpful* in controlling the acute manifestations of the disease Furthermore favorable results have been obtained with streptomycin-dihydrostreptomycin (2 Gm. daily intramuscularly) and sulfadiazine (4 to 6 Gm. daily orally in four to six equal divided doses) following the above dose schedule However this latter combination is possibly followed by a greater number of relapses *especially in cases due to Brucella suis*

Tularemia

Streptomycin represents the treatment of choice in all forms of tularemia. In the typhoid or pneumonic cases, *streptomycin 0 1 to 0.2 Gm is given every four to six hours* until the temperature has been normal for seventy-two hours with an average dose of 2 to 4 Gm. within five to seven days. Most cases will respond promptly on this regimen The dosage in ulceroglandular tularemia is less well established but, in general, smaller doses of streptomycin, 0 1 Gm. every four hours will usually prove effective On occasion the *Herxheimer type of reaction* will occur following streptomycin therapy especially if the tularemic exudates are large. In such cases one should consider treatment as effective and not an indication to increase the dosage of the drug The tetracyclines and chloramphenicol are also effective in tulare-

mia and with any of these agents the usual dose of drug is 250 to 500 mg. every four to six hours for six to ten days

Pinta

Penicillin has been used successfully in the treatment of this nonvenereal treponematosis. A single intramuscular injection of procaine penicillin in oil 1,200 000 units will produce complete healing of the active lesions in most instances within four to six months although the residual scarring of the disease may persist.

Scarlet Fever

Penicillin administered during the eruptive stage of scarlet fever tends to shorten the duration of fever free the throat of beta hemolytic streptococci and markedly decrease the incidence of suppurative sequellae. Penicillin is given orally 250 000 units every six hours or procaine penicillin 300 000 to 600 000 units daily or in cases where penicillin is contraindicated, tetracycline 500 mg. every six to eight hours. The treatment of established suppurative complications otitis media, sinusitis, meningitis, or empyema, is the same as in any other streptococcic infection

Infections Due to Bacteroides

Although infections due to the bacteroides group of organisms are considered rare they probably occur more frequently than is indicated by published case reports. No doubt some of them go unrecognized because of the difficulties associated with the isolation and identification of the offending organism and failure to consider anaerobic bacteria as the infecting agent. The genus *Bacteroides* includes a group of gram negative nonspore-forming highly pleomorphic obligate anaerobic bacilli the cultures of which are characterized by the fact that they may be negative at

forty-eight hours but positive at from four to eight days The usual source of infection by these organisms is presumed to be from the alimentary tract of the host from whence they are transported to other parts of the body by direct extension or by way of the blood and lymph. Not infrequently they are found in association with such other intestinal bacteria as *E coli Cl. perfringens* and anaerobic streptococci.

Bacteroides have been isolated from a variety of infections especially tonsillitis otitis media, lung abscess empyema, appendicitis, peritonitis, and endometritis Obviously when the organisms invade the blood stream, metastatic lesions may occur anywhere in the body the most frequent sites being in the lungs joints and liver Not infrequently *Bacteroides* infections have occurred in association with perforated diverticulitis and after resection of malignancy of the colon. Since these organisms constitute the dominant genus of the colon flora, such findings are not surprising. *Bacteroides* septicemia is sometimes found to be a complication of tonsillitis child birth, or abortion.

The successful treatment of infections due to the *Bacteroides* group depends upon (a) employment of an effective antimicrobial agent, or agents and (b) detection and eradication of all purulent foci. For the most part, penicillin and streptomycin, either alone or in combination, are relatively ineffective Isolated reports attest to the efficacy of large doses of sulfapyridines in cases of septicemia. The tetracyclines and chloramphenicol currently are regarded as the agents of choice (2 to 4 Gm. in divided doses daily)

Anthrax

Fortunately most cases of this disease represent the cutaneous type which responds strikingly to antimicrobial

therapy whereas the more severe forms anthrax bacteremia, or cases with pulmonary gastrointestinal or meningeal involvement, often expire within twenty four hours Penicillin represents the drug of choice in the treatment of anthrax (aqueous penicillin G 300 000 units every three to four hours) whereas larger doses (600 000 units every three hours) are employed in bacteremic cases or those with vesical involvement. Patients unable to take penicillin may be treated with one of the tetracyclines intravenously 500 mg every six to twelve hours in that excellent results have been obtained with these wide spectrum antibiotics especially in cutaneous anthrax in which cases the drugs are given by mouth (2 Gm in divided doses daily)

Diphtheria

Diphtheria has become so uncommon in this country that experience with the antimicrobial agents is very limited For the most part, penicillin has only been used in combination with antitoxin and this combination has been found to have little if any advantage over antitoxin alone in saving life and reducing complications In patients receiving the combination, the diphtheria organism shows a tendency to disappear from the nose and throat slightly earlier than in patients receiving antitoxin alone. Since there seems to be no adverse effect to penicillin it is of value in eliminating the carrier state and may be useful in patients sensitive to antitoxin the following would seem advisable Aqueous penicillin G 100 000 units every four hours or procaine penicillin 600 000 units for ten to twelve days

Yaws

Rapid clinical cures have been obtained with penicillin in the treatment of all stages of this treponemal infectious

disease. More recently satisfactory results have followed the use of chloramphenicol, chlortetracycline, and oxytetracycline, although comparative studies are as yet not available to ascertain the drug of choice. Penicillin G aqueous, 40 000 units intramuscularly every three hours for thirty doses, or 100 000 units daily for a total of 1,000 000 units, usually results in a rapid healing of the cutaneous lesions with the bone lesions responding within several weeks.

Plague

If antimicrobial therapy is started within the first twenty four hours in cases of pneumonic plague, the results are often satisfactory Streptomycin, 2 to 4 Gm. daily in divided doses intramuscularly is probably the most effective drug, although curative effects have been obtained with chloramphenicol (3 to 4 Gm. daily by mouth) and oxytetracycline (3 Gm daily by mouth in divided doses)

Rickettsial Diseases

The principal rickettsial diseases of Man are the typhus group which includes epidemic typhus murine typhus, Brill's disease, Rocky Mountain spotted fever rickettsialpox, tsutsugamushi disease (scrub typhus) and Q fever With the exception of rickettsialpox, this group of diseases represents serious conditions and best results with antibiotic therapy occur when it is instituted early in the disease process, coincident with the appearance of the rash. Both the tetracycline agents and chloramphenicol possess potent rickettsiastatic properties Thus far chlortetracycline appears to be the most proven antibiotic. In moderately severe cases, chlortetracycline orally 500 mg every four to six hours until the temperature has remained normal for forty-eight hours usually proves successful. Intravenous chlortetra

cycline (100 to 200 mg every six hours) is useful in comatose, uncooperative or nauseated patients until oral therapy can be safely instituted If the patient remains febrile for seventy two hours following specific therapy the possibility of a complication must be considered Relapses especially in cases with Q fever are best treated with the same antibiotic.

Weil's Disease (Leptospirosis)

Although experimental infections with *L icterohemorrhagica* have been successfully treated with penicillin streptomycin, or chlortetracycline and encouraging results have been reported with these drugs clinically especially chlortetracycline the status of the antibiotics in this disease is uncertain. However in view of a lack of a more effective form of treatment, it seems advisable to employ chlortetracycline 500 mg. every four hours (severe cases should receive 100 mg. intravenously every four hours) for ten to fourteen days

Rat Bite Fever (Haverhill Fever)

Antimicrobial therapy is indicated in cases of both the spirillar and bacillary forms of this disease Penicillin procaine 300 000 to 600 000 units daily or tetracycline or oxytetracycline 500 mg. every six to eight hours for seven to [illegible] days following the initial injury can be expected to prevent the development of systemic manifestations in most [illegible]stances. In cases of established systemic infection lar[illegible] doses of the drugs are indicated. Aqueous penicillin 300 000 units every four hours intramuscularly or [illegible]cycline or oxytetracycline 500 mg. every four hours [illegible] least ten to fourteen days (in that relapses are f[illegible]

Smallpox

The common complications of smallpox are largely due to the bacterial invasion of the vesicles and pustules particularly by the staphylococcus and streptococcus Although the antimicrobial agents have no influence on the toxemia resulting from the causative virus they are helpful in controlling the secondary bacterial infection Tetracycline or oxytetracycline 250 mg every four to six hours is recommended for the latter

Poliomyelitis, Acute Anterior

The antimicrobial agents have little usefulness in the management of acute poliomyelitis, but are indicated for the treatment of certain specific complications *e g* pulmonary and urinary tract infections Also these drugs should be given prophylactically in cases of urinary retention requiring an indwelling catheter (gantrisin 0.5 Gm every six hours or tetracycline or oxytetracycline 250 mg. every six to eight hours)

Measles

The incidence of secondary bacterial infections in measles has been markedly lessened with the use of the antimicrobial agents Since most of these complicating infections are due to the beta hemolytic streptococcus or pneumococcus penicillin orally 600 units per pound of body weight, every four to six hours or procaine penicillin intramuscularly 3000 units per pound of body weight daily will usually prove successful. In patients where penicillin is not possible, tetracycline or oxytetracycline, 5 mg per pound (11 mg per kg) of body weight, every four to six hours is recommended Should bacterial complications occur in spite of prophylactic therapy sensitivity studies should be performed immedi

ately Since bacterial complications are rarely encountered in German measles these drugs are not employed prophylactically but are used therapeutically when indicated

Hepatitis, Acute Infectious

The course of acute infectious hepatitis has not been shown to be influenced by the use of the antimicrobial agents. For the most part, their use is reserved for coincidental infections However they may be administered in severe cases in hopes of preventing pulmonary and urinary tract complications Furthermore in such cases many authorities are recommending cortisone and ACTH the use of which is attended by a lowering of resistance Chlortetracycline is given 500 mg every four to six hours by mouth or intravenous chlortetracycline 100 mg every four hours

Mononucleosis, Infectious

The results obtained with the antimicrobial agents in this infection have been uniformly disappointing, although chlortetracycline 500 mg. every four to six hours has been employed successfully in bacterial complications of this disease Furthermore in severe cases one is probably justified in combining antibiotic therapy with small doses (50-75 mg) of hydrocortisone

Cat Scratch Disease

This disease is thought by some to be caused by a virus related to the psittacosis lymphogranuloma venereum group and, although there is no solid evidence that the antimicrobial agents benefit this disease there is reason to believe that chloramphenicol (500 mg every four to six hours) when given early shortens the course of the infection and prevents suppuration of the involved lymph nodes

Systemic Fungous Infections

Most cases of superficial fungous infections will respond to various forms of local therapy however treatment of systemic mycoses presents a more difficult problem. Although many drugs have shown *in vitro* effectiveness against fungal infections in only two of this group of diseases (actinomycosis and nocardiosis) have the antimicrobial agents proved in any way effective. Actinomycosis has been successfully treated in some instances with penicillin (procaine penicillin intramuscularly 600 000 units daily without interruption for four to six weeks) Many investigators combine penicillin with sulfadiazine 1 Gm. every six hours until clinical improvement is definite and then 1 Gm. twice daily thereafter plus iodides and roentgen irradiation to accessible lesions In cases which fail to respond to the above regimen or in patients unable to take penicillin, other drugs such as streptomycin chloramphenicol, the tetracyclines and mycostatin, may be used. This same treatment is recommended for cases of nocardiosis in which disease sulfadiazine represents the drug of choice with one of the antibiotics as an adjunct. In both diseases *it is best to culture* the organism and perform sensitivity tests because of variable species susceptibility

Clostridial Infections
(Gas Gangrene, Tetanus, Botulism)

The genus *Clostridium* consists of predominantly gram positive bacilli which are anaerobic or micro-aerophilic and which produce spores. The natural habitats of these organisms are the soil and the intestinal tracts of man and animals. Clostridial species of medical importance can be roughly divided into three groups (a) Gas gangrene group (b)

Cl. tetani and (c) *Cl. botulinum*. The organisms within these groups all possess the ability to elaborate powerful exotoxins to which are referable the pathological changes observed in the respective disease processes

Gas Gangrene Group

The organisms primarily involved in gas gangrene are *Cl. perfringens (Cl. welchii) Cl. novyi (Cl. oedematiens) Cl. septicum (Vibrion septique* or *B oedematis maligni)* and *Cl. bifermentans (Cl. sordellii)* In about forty per cent of gas gangrene only one of these species is present, whereas mixed *Clostridia* are associated in about sixty per cent of cases *Cl. perfringens* is most frequently isolated from gas gangrene with *Cl. novyi* and *Cl. septicum* next in incidence. In view of this the antitoxins on the market are mixed polyvalent preparations in order to provide an antiserum which will afford protection against the three species

Cl. Tetani

Cl. tetani is the cause of the severe toxemia, known as tetanus a disease characterized by convulsive contraction of voluntary muscle. The organism is more fastidious in its anaerobic requirements than most of the gas gangrene species and morphologically shows the unique tennis racquet appearance due to the terminal location of its spore. Like the gas gangrene bacilli *Cl tetani* produce disease by the production of extracellular toxins known as haemotoxin and lethal neurotoxin.

Cl. Botulinum

C botulinum is the causative agent of botulism, a toxemia rather than an infection. Unlike the toxins produced by the gas gangrene and tetanus bacilli, botulinum toxin resists the

action of such proteolytic enzymes as pepsin and trypsin and therefore remains effective when ingested. In the main, botulism results from the ingestion of food containing toxin. Various strains of *Cl botulinum* produce specific toxins For some time two types A and B have been recognized, although more recently types C D and E, have been differentiated. The toxins act specifically on the myoneural junctions and cause death by bringing about respiratory paralysis

Therapy of Clostridial Infections

While sulfonamides penicillin, chloramphenicol, and the tetracyclines are effective against the bacilli *in vitro* they have little if any effect on the toxins elaborated by these organisms Hence antimicrobic therapy to the exclusion of antitoxin and surgical intervention, where indicated, cannot be relied upon as a completely adequate measure

In cases of gas gangrene, diagnosed on clinical or bacteriological evidence it is well to utilize a polyvalent antitoxin, either intravenously or intramuscularly prepared from antitoxin to *Cl. perfringens Cl novyi*, and *Cl. septicum* Penicillin should be given as adjunct therapy and indicated surgery instituted.

Botulinum antitoxin has not given the same favorable results as have been seen with the other clostridial antitoxins This in all probability has been due to the use of inadequate dosages

In tetanus antitoxin is not nearly as effective in established infections as it is when used prophylactically unless it is given in large doses simultaneously by various routes

Toxoids to induce active immunization, are available for gas gangrene tetanus and botulinum bacilli. Except for

tetanus where the role of toxoids has been unquestionably established their use in gas gangrene and botulinum is not usually justified in the former because of the lack of data on exposure of persons so immunized, in the latter because of the comparative infrequency with which the disease is seen at present

Relapsing Fever

At this time penicillin is considered the drug of choice in the treatment of relapsing fever although promising results have also been obtained with the tetracycline group of drugs In general a dosage of 500 000 to 1,000 000 units of crystalline penicillin G daily in four to six divided doses intramuscularly for seven days represents adequate therapy in most cases On occasion the Herxheimer type of reaction will occur following therapy Likewise chlortetracycline in a dosage of 3 Gm. daily at six hour intervals for seven to ten days has given satisfactory results and is recommended in patients sensitive to penicillin

Leprosy

Although many chemotherapeutic agents have been employed in the treatment of leprosy the most promising results have been obtained with the sulfones particularly dapsone Sulfone treatment appears to arrest the disease in practically every instance although it may take a very long time to accomplish this Furthermore when relapses occur they do so usually within the first year but remain amenable to subsequent retreatment The criteria for the therapeutic schedule varies with the type of case Lepromatous cases are treated until the disease is clinically inactive and all smears are bacteriologically negative in these cases a minimum period of treatment being twenty four

months In nonlepromatous cases treatment is continued for a minimum of one year More recently thiosemicarbazone has been used with encouraging results particularly in tuberculoid cases of leprosy Since the sulfones may give rise to certain toxic effects as a result of allergy such as exfoliative dermatitis and sometimes hepatitis, thiocarbazone may be used as an alternate remedy although it, too has limitations as regards toxicity and is not recommended for long term therapy

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Prophylactic Use of Antimicrobial Agents

The antimicrobial agents are employed prophylactically in a variety of conditions, ranging from the protection of the unborn to the prevention of complicating infections in the closing hours of life. In the terms of the tenderloin the prophylactic properties of these drugs represent the realization of a politician's dream, in that they offer protection to the individual from the womb to the tomb No doubt, many types of infections have been avoided by the judicious use of the antimicrobial agents but they have also been employed illogically which has added to their indiscriminate use. Certainly it seems advisable to limit their prophylactic use to those instances where the complication to be avoided is a serious one and one which occurs frequently in the absence of precautions At this time, evidence is sufficiently abundant to say that these drugs are of value and are indicated in certain specific instances

Prior to the advent of penicillin, it was known that small doses of sulfonamides (sulfadiazine 0.5 Gm. to 1 0 Gm. daily) would prevent streptococcal throat infections in a high percentage of patients and thus recurrences of rheumatic fever Likewise, penicillin 200 000 units twice daily by mouth or benzathine penicillin G 1,200 000 units intramuscularly every thirty days will give similar results More recently the tetracyclines (250 mg before breakfast and

after supper) has been used successfully and should be value in patients unable to tolerate penicillin or the sulf amides Regardless of the drug employed treatment is b continued throughout the year for five years following last attack of rheumatic fever and routinely to age eighte

Gonorrhea can usually be prevented by oral penicil 250 000 units if taken within six hours of exposure althou if used to the abandonment of mechanical and chemi prophylaxis will probably lead to an increase of other nereal diseases, especially syphilis Whereas oral prophyla for gonorrhea is sufficient, syphilis requires intramuscu penicillin 1,200 000 units for its prevention. Penicillin stilled into the eyes of a newborn child is an effect prophylaxis against conjunctivitis neonatorum Also pe cillin administered to an expectant mother with gonorrl and/or syphilis will prevent gonococcal complications the child as well as congenital syphilis

Many of the recent developments in surgery especia pulmonary and cardiac, have been aided by the prophylac value of these drugs in preventing infections following op ation The same holds true for many other types of surgi or obstetrical procedures. In patients undergoing la bowel resection the sparingly soluble sulfonamides s fasuxidine or sulfathaladine are administered for five d prior to operation, although one might question wheth the extent of sterilization thus obtained is of real significan More recently neomycin in combination with sulfasuxid has increased in popularity as a preoperative preparat measure in bowel surgery All patients with acquired congenital heart lesions in whom oral, rectal, colonic, transurethral operative procedures are contemplated shou receive prophylactic antimicrobial therapy before and af such operations

During outbreaks of meningococcal infections sulfadiazine or penicillin are effective prophylactic agents. In the management of chronic pulmonary disease the use of antimicrobial agents in the prevention and control of superimposed respiratory infections has proven valuable The same is true in diseases such as measles in which the bacterial complications are largely prevented by the use of these antimicrobial agents

One of the first duties of the physician is to educate the masses not to take medicine

SIR WILLIAM OSLER (1849–1919)

11

Antimicrobial Therapy — Looking Into The Future

The recent prodigious advances in this field exert a profound influence on the practice of medicine as within the span of less than a quarter of a century it has become possible to effect dramatic cures in a large percentage of patients suffering from diseases previously dreaded, as well as to prevent diseases which formerly proved disastrous Despite these advancements there remain many unsolved problems relating to antimicrobial therapy The big gaps are in the fields of viral, mycotic, protozoal, and parasitic diseases certain bacterial infections which as yet have eluded the action of these agents as well as an increasing number of bacteria which become resistant to these drugs No doubt it is but a matter of time before medical science finds the complete answer to these unsolved problems with their realization depending largely on the clarification of the mechanism by which these agents produce their effects From a thorough insight into this phenomenon will come the ability to construct chemotherapeutic agents for any and every infectious disease Furthermore, this knowledge will in turn define more clearly the antagonistic and synergistic action of these drugs and also may endow the clinician with drugs harmless to the patient and with possibly precise tissue specificity of action

Although many microorganisms if uncontrolled, are deadly enemies of Man, others are harmless and some are essential to Man s survival. Furthermore the antimicrobial agents like certain microorganisms are potentially harmful to Man, giving rise to a variety of untoward reactions some of which occur immediately while others appear long after their use many of which are mild, but some have proved fatal. Because of the diverse and peculiar nature of these side-effects it is impossible to estimate their true significance In view of the ability of these drugs to sensitize individuals we may see in the future an increasing number of more serious reactions following their use. Likewise more microorganisms may develop resistance to these agents Also the continued dislocation of the normal bacterial flora of the body by these drugs may result in more diseases due to organisms which at this time are not harmful and, at the same time may result in the destruction of bacteria which are helpful to Man in his own struggle for existence Therefore looking into the future we may find these antimicrobial agents will prove to be insidious purveyors of disease, in that Nature notoriously brooks interference badly and often in a subtle way defeats Man before he knows of his undoing Certainly the danger signals have been hoisted and, until the ideal agent is discovered, the physician should limit the use of these life-saving agents to diseases in which their therapeutic effectiveness has been demonstrated and to refrain from employing them prophylactically except when the complication to be avoided is a serious one and one which occurs frequently in the absence of precautions Finally despite the proven therapeutic value of the antimicrobial agents it is to be remembered that they are not

to be used to the exclusion or neglect of other proven forms of therapy

By observing simplicity in your prescriptions you will always have the command of a greater number of medicines of the same class, which may be used in succession to each other in proportion as habit renders the system insensible of their action.

BENJAMIN RUSH (February 7 1789)

Appendix

PARTIAL INDEX OF COMMERCIALLY AVAILABLE ANTIMICROBIAL AGENTS

An index of commercially available antimicrobial agents is here included. The rather large number of dosage forms of these agents now on the market precludes, for practical reasons, a complete and exhaustive listing. However the presentation of even a partial list showing representative preparations together with a specification of the active ingredients and manufacturer's name seemed desirable in view of its value as a readily available reference source to the busy practitioner and medical student. The omission of a product of any manufacturer is not intended to reflect on the value or reliability of the product.

Therapeutic Index—Partial Listing

ORAL PREPARATIONS

I Tablets and Capsules

Active Ingredients	*Trade Names*	*Indications*
Bacitracin 2500 u. Neomycin 25 u.	Bacimycin (Walker)	Bowel Surgery Intestinal infections
Carbomycin 100 mg.	Magnamycin (Pfizer)	Sensitive infections
Chloramphenicol 25-250 mg.	Chloromycetin (Parke Davis)	Sensitive infections
Chloramphenicol 125 mg. Dihydrostreptomycin 125 mg.	Kapseals Chlorostrep (Parke Davis)	Bowel Surgery
Chlortetracycline 50-250 mg.	Aureomycin (Lederle)	Sensitive infections
Chlortetracycline 125 mg. Triple sulfonamides 500 mg.	Aureomycin Triple Sulfas (Lederle)	Intestinal use
Erythromycin 100-200 mg.	Erythrocin (Abbott)	Sensitive infections
Erythromycin 100-200 mg.	Ilotycin (Lilly)	Sensitive infections
Erythromycin 50 mg. Triple sulfonamides 333 mg.	Ilotycin-sulfa (Lilly) Erythrocin with sulfas (Abbott)	Infections more susceptible to combination.
Erythromycin 100 mg. Triple sulfonamides 249 mg.	Erythrosulfas (Upjohn)	Infections more susceptible to combination.
Fumagillin 10 mg.	Fumidil (Abbott)	Intestinal amebiasis
Isoniazid 50-100 mg.	Cotenozin (Pfizer) INH (Lilly) Nicomyl (Parke Davis) Nydrazid (Squibb)	Tuberculosis
Mycostatin 500 000 u.	Nystatin (Squibb)	Intestinal Moniliasis
Neomycin 500 mg.	Mycifradin (Upjohn)	Bowel surgery

Active Ingredients	Trade Names	Indications
Neomycin 200 mg. Phthalylsulfathiazole 300 mg.	Sulfathaladine with neomycin (Sharp & Dohme)	Bowel surgery
Nitrofurantoin 100 mg.	Furadantin (Eaton)	Urinary infections
Oxytetracycline 50-250 mg.	Terramycin (Pfizer)	Sensitive infections
Oxytetracycline 100 mg. Polymyxin B 1000 units	Terramycin Polymyxin B (Pfizer) (vaginal tablets)	Vaginitis
DBED 100,000-200 000 u.	Bicillin (Wyeth)	Prophylaxis and sensitive infections.
DBED 200 000 units	Duapen—200 P A (Ayerst)	Prophylaxis and sensitive infections.
DBED 150 000 units Triple sulfonamides 500 mg.	Bicillin-sulfa (Wyeth) Duapen—S-150 (Ayerst)	Infections more susceptible to combinations.
Potassium Penicillin G 25 000-500 000 units	Celloral (Bristol) Oracillin (Merrill) Penoral (Wyeth) Pentids (Squibb)	Prophylaxis and sensitive infections.
Potassium Penicillin G 100 000-200 000 units Probenicid 250 mg.	Remanden (Sharp & Dohme)	Prophylaxis and sensitive infections.
Potassium Penicillin O 100 000 units	Cer-O-Cillin (Upjohn)	Penicillin-sensitive patient
Potassium Penicillin G 25 000-500 000 units Triple sulfonamides 200-500 mg.	Cellenta compound (Ayerst) Savorets (Lilly) Truo-cillin (Abbott) Celloral (Bristol) Biosulfa (Upjohn) Penicombisul (Schering) Pentresamide (Sharp & Dohme) Pentids sulfa (Squibb) sulfabiotic (Wyeth)	Infections more susceptible to combination.

Active Ingredients	Trade Names	Indications
Procaine Penicillin G 50 000-250 000 units	Pen. G Cap (Upjohn) Duracillin (Lilly) Ledercillin (Lederle)	Prophylaxis and sensitive infections.
Polymyxin B 500 000 units	Aerosporin (Burroughs Wellcome)	Bowel Surgery
Tetracycline 50-250 mg	Achromycin (Lederle) Tetracyn (Pfizer) Polycycline (Bristol)	Sensitive infections

Oral Sulfonamides

Active Ingredients	Trade Names	Indications
Para-aminobenzenesulfonamide 0 5 Gm	Sulfanilamide	Sensitive infections
2-sulfanilamido-pyrimidine 0.5 Gm	Sulfadiazine	Sensitive infections
Mono-methyl derivative of sulfadiazine 0 5 Gm.	Sulfamerazine	Sensitive infections
Dimethyl derivative of sulfadiazine 0.5 Gm.	Sulfamethazine	Sensitive infections
Sulfisoxazole 0.5 Gm.	Gantrisin (Hoffman La Roche)	Urinary infections
6 (Para aminobenzenesulfonamido) 2, 4-dimethyl pyrimidine 0.5 Gm.	Elkosin (Ciba)	Urinary infections
Phthalylsulfathiazole 0.5 Gm	Sulfathaladine	Bowel Surgery
Succinylsulfathiazole 0.5 Gm.	Sulfasuxidine	Bowel Surgery
Each 0.5 Gm. tablet contains 0 167 mg. (approx.) of sulfadiazine, sulfamerazine and sulfamethazine.	Sulfas-Triple	Sensitive infections

II Suspensions and Solutions

Active Ingredients	*Trade Names*	*Indications*
Chloramphenicol palmitate *125 mg. per 4 ml.*	Chloromycetin Palmitate (Parke Davis)	Pediatric use.
Chlortetracycline calcium 100 mg. per ml.	Aureomycin oral drops (Lederle)	Pediatric use
Chlortetracycline calcium 125 mg. per 4 cc.	Aureomycin syrup (Lederle)	Pediatric use
Dihydrostreptomycin 50 mg. per cc. Kaolin 480 mg. per cc. Pectin 40 mg. per cc.	Streptomagma (Wyeth)	Intestinal infections
Neomycin 300 mg. per fluid oz. *Kaolin 5832 mg. per fluid oz.* Pectin 13_ mg. per fluid oz.	Kaopectate with neomycin (Upjohn)	Intestinal infections
Oxytetracycline 100-200 mg. per cc.	Terramycin oral drops (Pfizer)	Pediatric use.
DBED 50 000-300 000 units per 5 cc.	Duapen suspension (Ayerst) Bicillin suspension (Wyeth) Permapen (Pfizer) Neolin (Lilly)	Prophylaxis and in sensitive infections.
DBED 150 000-300 000 units per 5 cc. Triple sulfonamides 500 mg. per 5 cc.	Bicillin sulfas suspension (Wyeth) Duapen-S (Ayerst) Sulfa-neolin (Lilly)	Infections more susceptible to combination
Potassium Penicillin G 50 000-500 000 units per 5 cc.	Cillenta (Ayerst) Dropcillin (White) Celloral (*Bristol*) Dramcillin (White) Sugracillin (Upjohn) Liquacillin (Lilly)	Prophylaxis and sensitive infections

Active Ingredients	*Trade Names*	*Indications*
Potassium Penicillin G 100 000-250 000 units per 5 cc. Triple sulfonamides 500 mg. per 5 cc.	Celloral (Bristol) Suspension Neopenzine (Lilly) Dramcillin (White) Liquid Tetracillin (Schering) Sulfonsol with penicillin (National) Sulfa-sucracillin (Upjohn)	Infections more susceptible to combination
Potassium Penicillin G 200 000 units per 5 cc. Gantrisin 500 mg. per 5 cc.	Gantricillin (Hoffman-La Roche)	Infections more susceptible to combination
Procaine Penicillin G 100 000-250 000 units per 5 cc. Triple sulfonamides 500 mg. per 5 cc.	Eskacillin-Sulfas (Smith, Kline & French)	Infections more susceptible to combination
Polymyxin B 125 000 units per 8 cc. Phthalylsulfacetamide 1000 mg. per 8 cc. Ion Exchange resins 10%, Synthetic sodium aluminum silicate 10%, synthetic magnesium aluminum silicate 1.25% Parahydroxybenzoates 0 3%	Resion-P.M.S (National)	Intestinal infections
Streptomycin 50 mg. per cc.	Strycin sulfate (Squibb)	Bowel Surgery
Tetracycline 250 mg per 5 cc.	Tehacyn Oral Suspension (Pfizer) Achromycin Oral Suspension (Lederle)	Pediatric Use

ORAL SULFONAMIDES

Active Ingredients	*Trade Names*	*Indications*
Sulfasuxidine 10%, Pectin 1%, Kaolin 10% 0.5 Gm. per 5 cc.	Cremosuxidine (Sharp & Dohme)	Intestinal infections
Microcrystalline sulfadiazine 0.5 Gm. per 5 cc.	Eskadiazine (Smith, Kline & French)	Sensitive infections
Microcrystalline sulfamethazine, sulfamerazine sulfadiazine 0 167 Gm. each per 5 cc.	Liquid Metha Merdiazine (McNeil)	Infections more susceptible to combination
Sulfadiazine and sulfamerazine 0 15 Gm. each per 5 cc	Duozine (Abbott)	Infections more susceptible to combination
Sulfamerazine 100 mg., Sulfamethazine 200 mg., Sulfadiazine 200 mg. per 5 cc.	Crematres (Sharp & Dohme)	Infections more susceptible to combination
Sulfadiazine Sulfamethazine, Sulfamerazine 0 167 Gm. each per 5 cc.	Triple Sulfas Suspension (Lederle) Cocosulfonamide Triplex (Lilly) Terfonyl (Squibb) Sulfose (Wyeth)	Infections more susceptible to combination

PARENTERAL PREPARATIONS

Active Ingredients	*Trade Names*	*Indications*
Bacitracin 60 000 units vial	Parentracin (C.S C)	Selected resistant organisms
Chloramphenicol 500 mg. per 2 cc.	Chloromycetin parenteral (Parke Davis)	Intravenous
Chloramphenicol 1000 mg. per vial	Chloromycetin parenteral (Parke Davis)	Intramuscular
Chlortetracycline 100-500 mg. vials	Aureomycin intravenous (Lederle)	Intravenous
Dihydrostreptomycin 1 Gm vial	Dihydrostreptomycin sulfate (Squibb)	Sensitive infections
Dihydrostreptomycin 500 mg. per cc.	Dihydrostreptomycin sulfate solution (Squibb)	Sensitive infections

Active Ingredients	*Trade Names*	*Indications*
Erythromycin 250 mg. vial	Ilotycin glucoheptonate ampoule (Lilly)	Intravenous
Chloroprocaine penicillin O 300 000 units per cc.	De Po-Cer-O-Cillin (Upjohn)	Patients sensitive to Penicillin G
Oxytetracycline 250-500 mg. vial	Terramycin intravenous (Pfizer)	Intravenous
Oxytetracycline 100 mg. vial	Terramycin intramuscular (Pfizer)	Intramuscular
DBED 600 000 1,200 000 units per cc.	Bicillin (Wyeth)	Prophylaxis and penicillin-sensitive infections
DBED 600 000 units Procaine penicillin G 300 000 units, Potassium penicillin G 300 000 units per cc.	Bicillin all Purpose (Wyeth) Duapen Forte (Aqueous) (Ayerst) PanBiotic (Bristol)	Prophylaxis and Penicillin-sensitive infections
DBED 600 000 units, Procaine penicillin G 300 000 units, Potassium penicillin G 100 000 units per cc.	PanBiotic (Bristol) Permapen Fortified (Pfizer)	Prophylaxis and Penicillin sensitive infections
1-ephenamine penicillin G 300 000 units	Compenamine (C.S C)	Penicillin-sensitive patient
Potassium penicillin O 200 000-500 000 units per vial	Cer-O-Cillin (Upjohn)	Penicillin-sensitive patient
Procaine penicillin 300 000-600 000 units Potassium or Sodium penicillin 100 000-200 000 units, Dihydrostreptomycin 0.5-1 0 Gm. per cc.	Cillimycin (Wyeth) Combiotic (Pfizer) Dicrysticin (Squibb) Dihydrocillin (Upjohn) Penstrep (Merck) Sharcillin (Sharp & Dohme)	Sensitive infections

Active Ingredients	*Trade Names*	*Indications*
Procaine penicillin G 300 000 units, Potassium penicillin G 100 000 units, dihydrostreptomycin 250-500 mg., streptomycin 250-500 mg per cc.	Durycin (Lilly)	Sensitive infections
Hydriodide of Diethylaminoethyl ester of Penicillin G 500 000 units per vial	Neo-Penil (Smith, Kline & French)	Sensitive pulmonary infections
Crystalline Potassium Penicillin G 200 000-5 000 000 units		Sensitive infections
Procaine Penicillin 300 000-1 000 000 units per cc	Crysticillin (Squibb) Diurnal-penicillin (Upjohn) Duracillin (Lilly) Sharcillin (Sharp & Dohme)	Sensitive infections
Procaine Penicillin 300 000-900 000 units, Potassium Penicillin 100 000-300 000 u.	Crystifor (Squibb) Abbocillin (Abbott) Wycillin Fortified (Wyeth) Sharcillin Fortified (Sharp & Dohme) Diurnal penicillin Fortified (Upjohn) Duracillin (Lilly) Ledercillin Parenteral (Lederle) Pronapen (Pfizer)	Sensitive infections
Procaine Penicillin 300 000-400 000 units, Dihydrostreptomycin 0 3-1 0 Gm per cc.	Aqueous suspension Penstrep (Merck) Combiotic aqueous suspension (Pfizer) Dihydrocillin readimixed (Upjohn) Distrycillin (Squibb) Duracillin—A.S in dihydrostreptomycin (Lilly)	Sensitive infections

Active Ingredients	Trade Names	Indications
Procaine Penicillin 300 000-600 000 units, Dihydrostreptomycin, 0 15-0.5 Gm Streptomycin 0 15-0.5 Gm.	Durycin (Lilly) Crysdimycin (Squibb)	Sensitive infections
Polymyxin B 500 000 units per vial	Aerosporin (Burroughs Wellcome)	Sensitive infections
Streptomycin 0.5 Gm. per cc Dihydrostreptomycin 0.5 Gm. per cc.	Combistrep (Pfizer) Distreptocin (Lilly) Distrycin (Squibb) Duo-strep (Merck)	Sensitive infections
Sulfadiazine sodium, 5 per cent solution		Intravenous
Sulfanilamide, 1 per cent solution		Intravenous or subcutaneous
Streptomycin 1 Gm. per vial, Isoniazid 236 mg per vial	Streptohydrazid (Pfizer)	Tuberculosis
Tetracycline 100-500 mg. vials	Achromycin intravenous (Lederle) Tetracyn intravenous (Pfizer)	Sensitive infections
Tetracycline 100 mg. vials	Achromycin intramuscular (Lederle) Tetracyn intramuscular (Pfizer)	Sensitive infections
	TOPICAL PREPARATIONS	
Bacitracin 300 units per gm. Neomycin 5 mg. per gram	Mycitracin (Upjohn)	Ointment
Bacitracin 500 units per gm	Baciguent (Upjohn) Bacitracin Ointment (Lilly)	Ointment
Bacitracin 500 units per Gm. Cortone 15 mg. per gram	Bacitracin with cortone (Merck)	Ocular infections

Active Ingredients	*Trade Names*	*Indications*
Bacitracin 500 units per gm. Polymyxin B 10 000 units per gm.	Polysporin (*Burroughs-Wellcome*)	Topical and ocular infections
Tyrothricin 500 mcgm per gm. Bacitracin 500 units per gm.	Tyrotrace (Sharp & Dohme)	Topical and ocular infections
Bacitracin 25 000 units per tablet	Solvets (Lilly)	Ocular infections
Chloramphenicol 10 mg. per gm.	Chloromycetin ointment (Parke Davis)	Topical and ocular infections
Chlortetracycline 16 gm. of 2% ointment per dressing	Aureomycin dressing (Davis & Geck)	Topical use
Chlortetracycline 10-30 mg. per gram	Aureomycin ointment (Lederle)	Ointment
Chlortetracycline 25-50 mg. per vial	Aureomycin Ophthalmic (Lederle)	Ocular and Otic
Chlortetracycline 100-250 mg. per suppository	Aureomycin vaginal suppositories (Lederle)	Vaginitis
Erythromycin 5-10 mg. per gm.	Erythroguent (Upjohn) Erythrocin Ointment (Abbott) Ilotycin Ointment (Lilly)	Ointment
Neomycin 5 mg. per gm., Cortisone 15 mg. per gm	Neosone Ophthalmic (Upjohn)	Ocular infections
Neomycin 2.5 mg. per gm., Gramicidin 0 25 mg. per gm	Streptocin ointment (Squibb)	Ointment
Oxytetracycline 1-30 mg. per gram	Terramycin ointment (Pfizer)	Ointment
Oxytetracycline 25 mg. per vial	Terramycin ophthalmic solution (Pfizer)	Ocular and Otic
Oxytetracycline 100 mg. per tablet	Terramycin vaginal tablets (Pfizer)	Vaginitis
Polymyxin B 200 000 units per vial	Aerosporin sterile (Burroughs-Wellcome)	Topical
Dihydrostreptomycin 500 mcgm. per gram	Dihydrostreptomycin ointment (Bristol)	Ointment

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CHAPTER I

Antimicrobial Agents

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